Contents

serotonin and norepinephrine

THE NEUROHORMONAL CONCEPT

The concept of "functional" diseases of the central nervous system is an old one. Failure to demonstrate pathology, even in major psychoses, is responsible for persistence of this concept. During the life, or after the death, of patients with schizophrenia or manic-depressive psychosis, pathologists are unable to confirm the diagnoses. Because structural changes are not discernible at a cellular level, it is at the molecular or biochemical level that investigators are apparently opening a new era in psychiatry.[1]

The posterior pituitary hormones are ready evidence that nerve cells may secrete true hormones.[2] In attempting to probe the enigma of mental illness, the study of neurosecretions, or neurohormones —as they are recognized by some investigators—has become increasingly important. Until recently only acetylcholine has been positively identified as a neurohormone for the central nervous system. In view of the fact that some areas of the brain have little or no acetylcholine, it has been difficult to explain diverse effects of drugs by the action of this mediator alone.

Recently two biologically active amines, serotonin and norepinephrine, were discovered to be present in uneven distribution in the brain. Brodie, Prockop and Shore[3] consider it "reasonable to assume that serotonin and norepinephrine have a specialized function in the areas where they are found." The amounts of these substances in the brain and their interrelationships are considered by many to be essential determinants of psychiatric symptomatology.

SEROTONIN

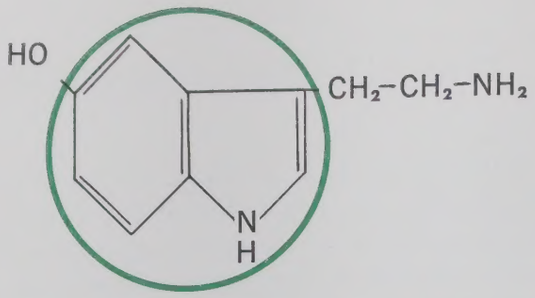
General Considerations

Serotonin is new only in consideration of its relationship to brain processes; it has been known for over one hundred years and recognized for a long time as a potent vasoconstrictor substance present in the blood platelets.[4,5] Recognition of its presence in the brain has stimulated interest concerning its role in the central nervous system. That the amount of serotonin in the brain may be related to the symptomatology of mental illness was postulated by Woolley and Shaw[6] in 1954. This followed their observation on experimental animals, that antimetabolites of serotonin, such as LSD and yohimbine, caused "mental aberrations."[6]

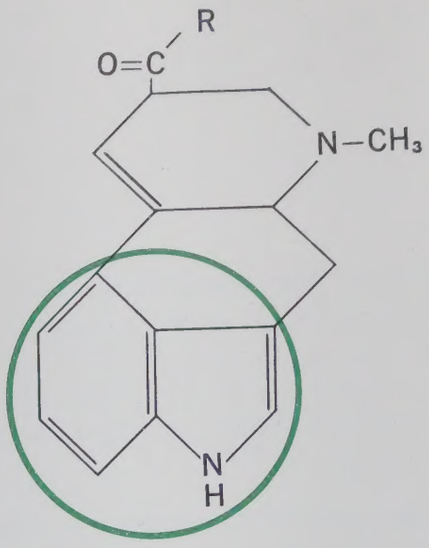
Distribution of serotonin in the brain parallels closely that of norepinephrine, with the primitive areas of the brain, such as the midbrain and hypothalamus, having the greatest concentrations. Presence of the substance is demonstrated by spectrophotofluorimetry and by bioassay procedures.[7]

Chemistry and Metabolism

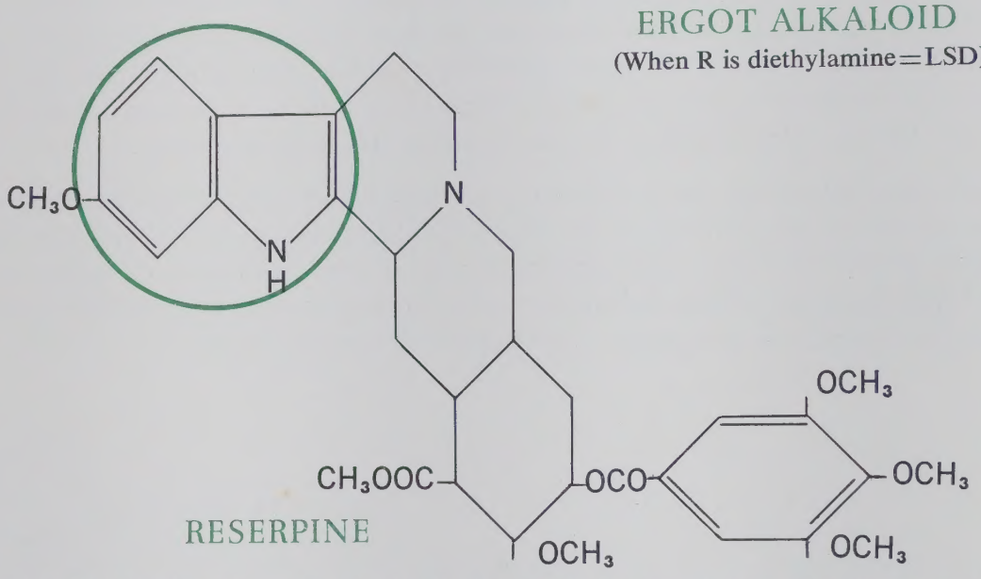
It has been suggested that the actions of psychopharmacologic agents may be related to their structure. Thus the presence in common of the indole nucleus has been noted in reserpine and in the psychotomimetic, lysergic acid diethylamide (LSD), as well as in serotonin. (See accompanying illustration.)



SEROTONIN
(5-hydroxytryptamine)



ERGOT ALKALOID
(When R is diethylamine=LSD)



RESERPINE

The metabolism of serotonin is still under study. Evidence indicates that serotonin is synthesized in the brain from a precursor, the amino acid 5-hydroxytryptophane. An enzyme, monoamine oxidase, acts on serotonin as substrate and seemingly is responsible for its degradation; it is excreted in the urine as 5-hydroxyindoleacetic acid.[8] Monoamine oxidase is significant in psychopharmacology since it may be inhibited by certain drugs such as iproniazid. Experimental studies suggest that serotonin is rapidly turned over in the brain.[7]

Evidence for Serotonin Action in the Brain

Serotonin may be implicated in schizophrenia; some workers believe that this illness is related to serotonin-deficiency, and others speculate that it is an excess of serotonin that causes the characteristic symptoms.[9] Fazekas[10] believes that, although ample evidence exists for its peripheral activity, the central function of serotonin has not been clearly defined.

The contractile effect of serotonin on smooth muscle is a well-studied manifestation of its action. Woolley,[11] observing the effect of serotonin on human and rat brain tissue cultures *in vitro,* reported a contractile effect on the oligodendroglial cells and concluded that this action on the brain "is possibly one of many."

Experimental observation is hindered by the inability of serotonin to pass the blood-brain barrier, even when serotonin blood levels are one hundred times the normal, such as in malignant carcinoid. Direct injection of serotonin into an animal brain produces drowsiness, lethargy and an unwillingness to perform normal movements.[11] Administration of large doses of its precursor, 5-hydroxytryptophane, to animals increases brain serotonin concentration and causes generalized somatic, autonomic and behavioral reactions.[10]

SOME EFFECTS OF 5-HYDROXYTRYPTOPHANE IN THE DOG*

(intravenous administration 60 mg./Kg.)

Generalized skeletal muscle tremors
Loss of placing reactions
Postural incoordination
Salivation
Piloerection
Lacrimation
Increased heart rate
Loss of response to visual stimuli
Increased gastrointestinal activity
Pupillary dilation
Loss of the light reflex

*Adapted from Udenfriend, Weissbach and Bogdanski.[7]

Another body of evidence pointing to serotonin participation in mental processes is the study of its antimetabolites. It is postulated that a structural analogue of serotonin, as LSD, for instance, may replace it in some essential metabolic process, giving rise to psychotic-like symptoms. As additional evidence for the participation of serotonin in brain activity, many of the psychotherapeutic drugs have been shown to influence the action of serotonin, while producing a favorable effect on mental symptoms.[11]

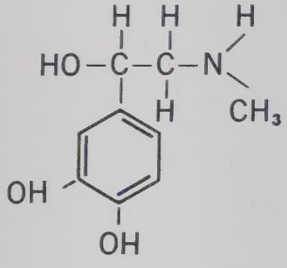
Bulle and Konchegul[12] have reported the occurrence of reflex changes in a dog following the administration of cerebrospinal fluid from schizophrenic patients, these changes being identical to those caused by serotonin. They conclude that "a neurohumor with identical neurotropic properties, as serotonin, is involved in the pathology of schizophrenic psychoses."[12]

NOREPINEPHRINE

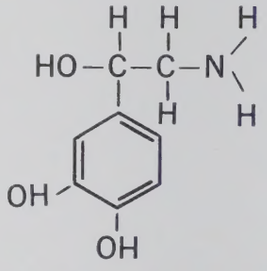
General Considerations

Peripherally, norepinephrine is found together with epinephrine in the adrenal medulla as well as in adrenergic nerves and neurons.[5] However, norepinephrine, unlike epinephrine, has been found to be present in some quantity in the brain, especially in those areas like the hypothalamus which are concerned with autonomic regulation.[4,13] Believed to be a derivative or degradation product of epinephrine, norepinephrine as well as adrenochrome and adrenolutin, both oxidation products of epinephrine, are all being studied as to their psychopharmacologic significance. Experimentally adrenochrome and adrenolutin have been found to be psychotomimetic, thus suggesting that abnormal amounts of endogenous metabolites in some patients may act to cause clinical psychosis. Since the amount of norepinephrine greatly exceeds the amount of epinephrine in the brain, it is believed that norepinephrine derivatives "...eventually may turn out to be of more interest than those of epinephrine as possible endogenous agents responsible for clinical psychoses."[13]

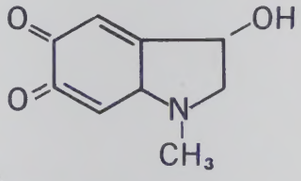
Chemistry and Metabolism



EPINEPHRINE



NOREPINEPHRINE



ADRENOCHROME

There is good evidence to indicate that brain norepinephrine is made in the brain itself. Like serotonin, norepinephrine appears to be stored in an inactive form, suggesting that perhaps a nerve impulse releases the free active form.[3] The enzyme, monoamine oxidase, is thought to act on this amine as it does on serotonin, causing physiological inactivation.[3] The possible endogenous psychotogenetic role of degradation products of epinephrine and norepinephrine has already been mentioned.

Evidence for Norepinephrine Role in the Brain

Experimental studies with these compounds present considerable problems.[14] Besides being difficult to synthesize, adrenergic substances such as adrenochrome and adrenolutin are unstable and the psychotogenic changes they induce are often too subtle to detect and measure. Although the evidence is not as extensive as obtained for serotonin, nevertheless some investigators believe there is enough to suggest a role for norepinephrine and/or its degradation products in brain activity.

Initial interest in this group of compounds as possible endogenous factors in psychosis was partly due to the chance recognition by an anesthetist, of psychologic disturbances from a deteriorated epinephrine solution. Later, this deteriorated solution was found to contain adrenochrome.

Osmond[14] believes that this compound and adrenolutin are psychotomimetic. In 1954 Osmond, with Hoffer and Smythies,[15] injected adrenochrome into human beings and reported the development of schizophrenic-like symptoms in their subjects.

It had long been recognized that asthmatic patients sometimes experienced abnormal mental symptoms with administration of epinephrine; Lindemann called attention to the aggravation of symptoms when schizophrenic patients were injected with epinephrine.[16] Rothballer[17] reported that the intravenous injection of norepinephrine in laboratory animals produced excitation as well as an EEG arousal pattern. Elmadjian's studies, in man, of the excretion and metabolism of epinephrine and norepinephrine "have suggested a differential pattern depending upon the emotional reaction of the subject."[18] The former is associated with the passive-anxious-fearful response, and norepinephrine with the aggressive-active-hostile response.

MECHANISMS AND THEORIES

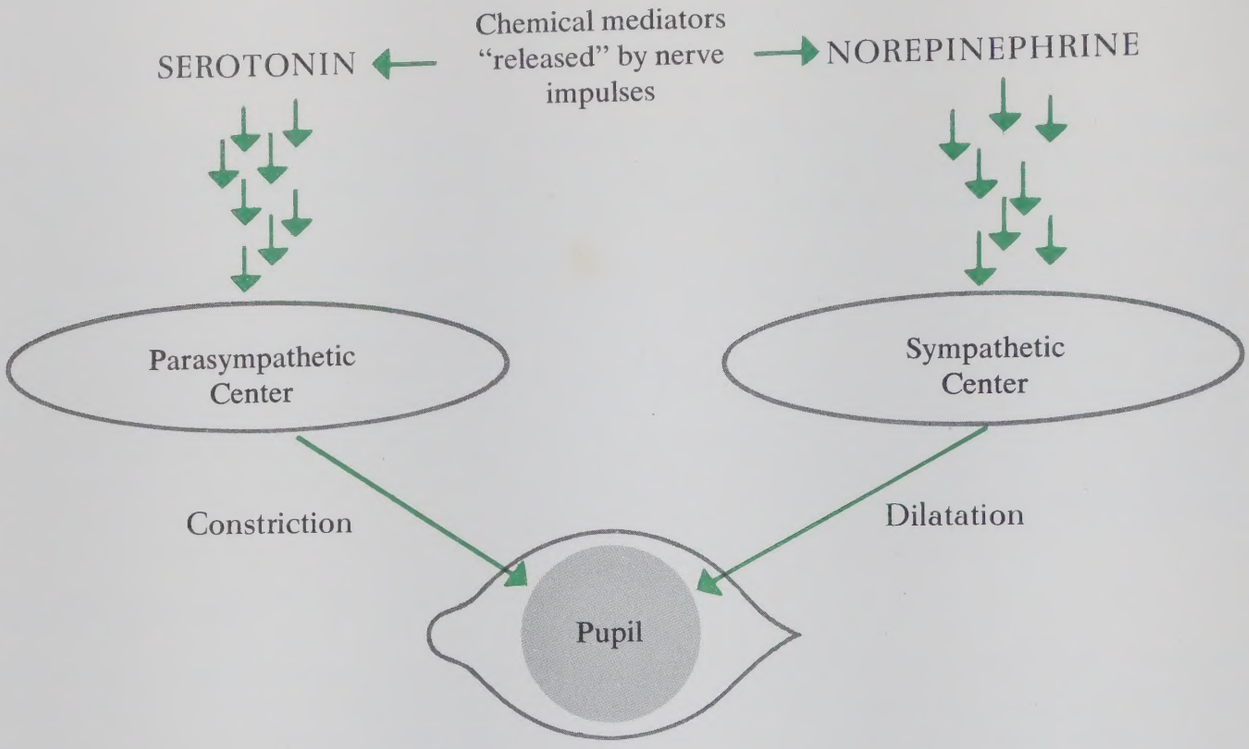
Marrazzi[19] has used the brain of a cat to measure the effects of these neurohumors on cerebral synapses. The basic technique used is the application of an electrical stimulus to one optic cortex which evokes a cortical potential in the contralateral cortex after transmission across a synapse. He found that cerebral synaptic transmission was considerably inhibited by serotonin, less so by norepinephrine and epinephrine. "The great effectiveness of serotonin [in causing synaptic inhibition] not only suggests that this is the type of chemical structure implicated... but that it constitutes one link, another being its natural occurrence in the brain, in the chain of evidence identifying it as a cerebral neurohumor."[19] Thus, a derangement of normal neurohumoral balance at brain synapses was suggested as a potential mechanism of mental derangement.[19] The psychotomimetic substances, such as LSD and mescaline, which resemble the neurohumors structurally, have similarly been shown to inhibit synaptic transmission. This finding lends additional support to this theory of the etiology of mental illness.

The Ergotropic and Trophotropic Concept

The physiologic concepts of Hess,[20] by suggesting a function for brain serotonin and norepinephrine, are helpful in providing a working hypothesis of the possible modes of action of a number of centrally acting drugs. Similar to the sympathetic and parasympathetic divisions of the autonomic nervous system, Hess postulated existence of a subcortical system, the function of which is to integrate autonomic, psychic and somatic functions. This subcortical system, he further suggested, has two antagonistic subdivisions:

1. Ergotropic—subserved by norepinephrine—predominance causes excitement.
2. Trophotropic—subserved by serotonin—predominance causes apathy.

Brodie and Shore[21] have presented a simplified schematic diagram based on the concept of antagonistic brain centers.



Diagrammatic representation of mutually antagonistic brain centers in the central autonomic nervous system. (Adapted from Brodie, B. B., and Shore, P. A.[21])

Drugs may thus act on the brain by being serotonergic (trophotropic), adrenergic (ergotropic—stimulating norepinephrine production) or by blocking either of these centers.[21] Thus, reserpine is thought to produce its effects by releasing free serotonin, and the phenothiazines, as TRILAFON, by blocking the action of norepinephrine (adrenergic blockade).

IMPLICATIONS IN MAN

This summary of the work on these substances is by no means the final word, and the status of serotonin and norepinephrine must needs be presented in a rather simplified fashion. Because of the difficult problems of clinical approach, almost all of the experimental work has been done on animals. However, the techniques of the biochemist and pharmacologist are being used in human studies as well as animal studies to determine the action of these agents, both those involved in metabolic processes and those produced by chemists. In psychiatric research, psychopharmacologic investigations in man are essential since "...one cannot predict from animal work the complex emotional and neurophysiologic responses of man."[22]

Although the results and concepts presented here are not equally acceptable to all psychiatrists, and the laboratory and experimental findings have still to be coordinated in many instances, there is a general impression that we are on the threshold of a major breakthrough in psychiatry. In the search for possible deficiencies in the brain of the mentally ill, in the therapy of mental illness itself, and by the study of model psychoses, progress continues to be made.[9]

Bibliography: (1) Saunders, J. C.: Some Chemical Concepts in Psychosomatic Medicine, presented at 5th Ann. Meet., Academy of Psychosomatic Medicine, New York, Oct. 9-11, 1958. (2) Blaschko, H., in Garattini, S., and Ghetti, V.: Psychotropic Drugs, Amsterdam, Elsevier Publishing Company, 1957, p. 3. (3) Brodie, B. B.; Prockop, D. J., and Shore, P. A.: Postgrad. Med. *24*:296, 1958. (4) Domino, E. F., in Jasper, H. H., and others: Reticular Formation of the Brain, Boston, Little, Brown & Company, 1958, p. 285. (5) Sollmann, T.: A Manual of Pharmacology, ed. 8, Philadelphia, W. B. Saunders Company, 1957, pp. 499-502. (6) Woolley, D. W., and Shaw, E.: Science *119*:587, 1954. (7) Udenfriend, S.; Weissbach, H., and Bogdanski, D. F.: Ann. New York Acad. Sc. *66*:602, 1957. (8) Page, I. H.: *ibid.*, p. 592. (9) Malitz, S.: New York J. Med. *57*:3293, 1957. (10) Fazekas, J. F.: Am. J. Med. *25*:89, 1958. (11) Woolley, D. W., in Pennes, H. H.: Psychopharmacology, New York, Harper & Brothers, 1958, p. 152. (12) Bulle, P. H., and Konchegul, L.: J. Clin. & Exper. Psychopath. *18*:287, 1957. (13) Hoagland, H.: Ann. New York Acad. Sc. *66*:445, 1957. (14) Osmond, H.: *ibid.*, p. 418. (15) Hoffer, A.; Osmond, H., and Smythies, J., cited in Marrazzi, A. S.: Ann. New York Acad. Sc. *66*:496, 1957. (16) Lindemann, E., cited in Malitz, S.: New York J. Med. *57*:3293, 1957. (17) Rothballer, A. B., cited in Brodie, B. B.; Prockop, D. J., and Shore, P. A.: Postgrad. Med. *24*:296, 1958. (18) Elmadjian, F., cited in Fazekas, J. F.: Am. J. Med. *25*:89, 1958. (19) Marrazzi, A. S.: Ann. New York Acad. Sc. *66*:496, 1957. (20) Hess, W. R., cited in Brodie, B. B.; Prockop, D. J., and Shore, P. A.: Postgrad. Med. *24*:296, 1958. (21) Brodie, B. B., and Shore, P. A.: Ann. New York Acad. Sc. *66*:631, 1957. (22) Ewing, J. H.; Rickels, K.; Werntz, J. L., and Lakke, J. P.: J. M. Soc. New Jersey *54*:573, 1957.

2

THE PSYCHOTOMIMETIC DRUGS—MESCALINE AND LSD

The recently reawakened interest in psychopharmacology has stimulated more intensive research into the basic nature of the so-called "functional" disorders. The absence of microscopically or macroscopically detectable brain lesions has encouraged a search for molecular determinants to supply the clue to our understanding of the schizophrenic process.[1] Psychotomimetic agents, such as LSD and mescaline, are important psychiatric experimental tools because of their ability to "open new channels for the investigator."[1]

"The difficulty in producing major psychic disorders in a controlled laboratory setting has long hindered the understanding and development of a rational therapy in psychiatry."[2] However, with the artificial induction of abnormal states, investigators may now observe and compare phenomena with bearing on the origin, meaning and therapy of symptoms.[2]

WHAT IS A PSYCHOTOMIMETIC DRUG?

According to Malitz,[3] "The major quality of the hallucinogens is their ability to produce psychotic phenomena in the presence of a clear sensorium." His phrase is significant in differentiating the psychotomimetic effects of these compounds from those produced by many sedative or narcotic substances, such as opium, chloral hydrate or barbiturates, which cloud consciousness or even render the patient unconscious.[4] Hoffer and his associates[5] similarly refer to the ability of these compounds to produce hallucinations "without other disturbing symptoms."

Although a number of other hallucinogens (a term frequently used to describe these drugs), both natural and synthetic, also has been studied, mescaline and lysergic acid diethylamide (LSD) have been most intensively investigated.[3] These psychotomimetic compounds, according to a recent evaluation in a round-table discussion of the American Psychiatric Association, produce schizophrenic-like symptoms but "do not produce the total schizophrenic personality change."[2]

LYSERGIC ACID DIETHYLAMIDE (LSD)

Background

In 1943, Hofmann, a Swiss chemist, noticed peculiar sensations while working on the synthesis of the ergot derivative, lysergic acid diethylamide. In his words,[6] "Objects in my vicinity and also the shape of my co-workers in the laboratory appeared to undergo optical changes. I was incapable of concentrating my mind on my work....With closed eyes [he had returned home to sleep] fantastic pictures of extraordinary plasticity and intensive kaleidoscopic colorfulness seemed to surge towards me." After a few hours he returned to a normal state.

Three days later symptoms reappeared with greater intensity after self-administration of 250 micrograms of LSD. Recognition of the behavioral similarities to schizophrenia led to further investigations of this compound; the first studies in the United States were undertaken in 1949.[2]

Chemistry and Metabolism of LSD

Lysergic acid diethylamide is a typical semisynthetic amide of the ergot group of alkaloids.[6] It is a chemical linkage of lysergic acid, derived from the natural ergot alkaloids, with the diethyl amino group.[7] The indole nucleus, which has been emphasized in the accompanying figure, is also found in other compounds (such as serotonin and reserpine) affecting the psyche.

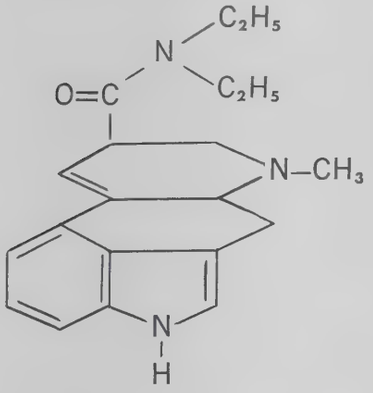


Fig. 1. Lysergic Acid Diethylamide (LSD)

The dose of LSD required to produce symptoms is minute, 100 to 200 micrograms. Unlike mescaline, which is usually administered intravenously, LSD is given orally, although it has also been given intrathecally and intravenously.[3] Much of its metabolic cycle is still unsolved.[6] Like mescaline, LSD is distributed to all tissues, with the lowest concentration found in the brain.[2]

Pharmacology of LSD

The multiple pharmacological actions of LSD—psychic, motor, autonomic—are illustrated in the accompanying figure. Its antiserotonin effect[8] is probably its most significant property. Following the suggestion of Hess[9] (as discussed in the first monograph in this series), LSD and mescaline may be characterized as ergotropic in their action; that is, they "produce excitement and increased sympathetic activity, sensitivity to external stimuli, and skeletal muscle tone."[10] Rothlin believes that future clinical investigation should be directed toward analysis of the autonomic manifestations,[11] which would further better understanding of their relation to psychic changes.

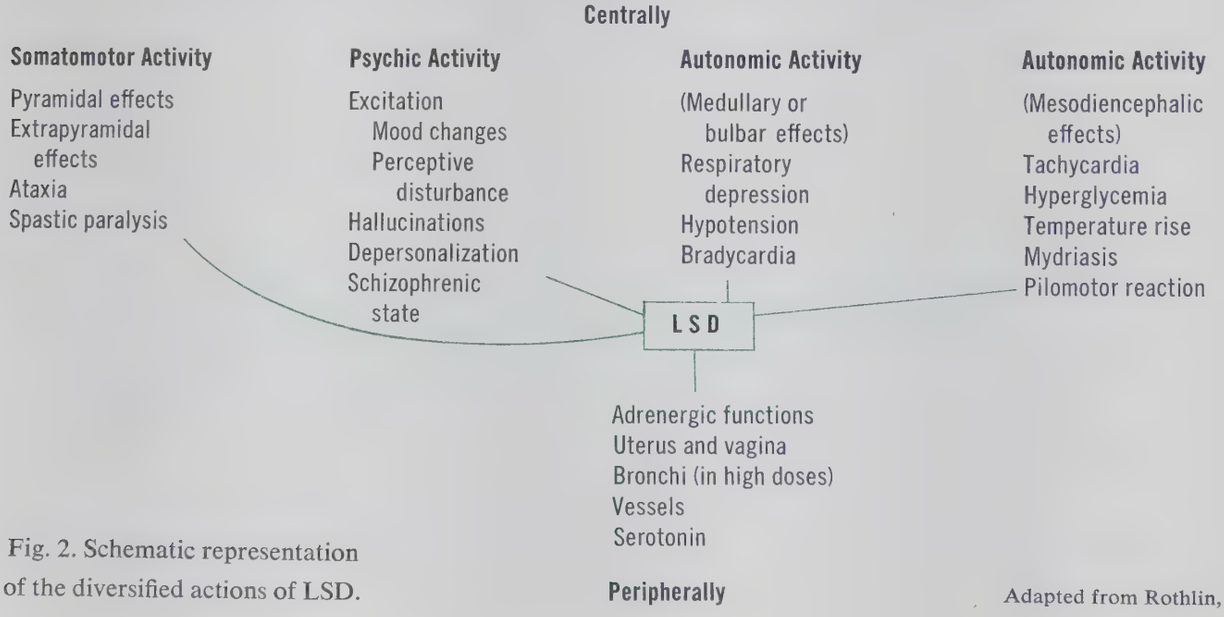


Fig. 2. Schematic representation of the diversified actions of LSD.

Adapted from Rothlin, E.[11]

There is a marked structural specificity to the effects of LSD, since the slightest molecular modification reduces its effectiveness greatly.[6] Rapid development of tolerance on repeated administration has been reported by several investigators.[12-14]

MESCALINE

Background

The psychotomimetic effects of mescaline have been employed for centuries in the religious rites of the Southwest Indians[3] who chew it in its native form of peyotl cactus to achieve the hallucinatory state. Addiction has not been reported.[15] The pure alkaloid was isolated in 1894 and it was probably the first of these compounds to be synthesized.

Chemistry and Metabolism of Mescaline

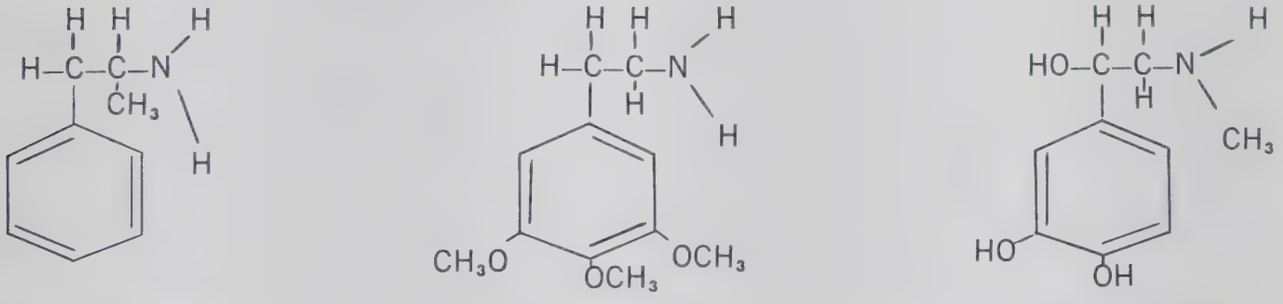


Fig. 3. Structural similarity of mescaline to other compounds.

Although structurally dissimilar to LSD, mescaline is similar in effects.[6] Some findings suggest that mescaline must be converted into another compound to produce its effects.[8] It is rapidly excreted in urine, partly as the metabolic product, 3,4,5-trimethoxyphenylacetic acid.[15] Tolerance to the compound has been reported following repeated dosage; this disappears if administration is temporarily suspended.[16]

Pharmacology

Mescaline may be given intravenously for immediate effect or orally (½-¾ Gm.) with onset of action in one-half hour. The autonomic and vegetative disturbances following mescaline administration are similar to, but generally more intense than, LSD. As with LSD,[3] there are also disturbances in perception, mental control and emotions.[17]

Chemical similarity to epinephrine led Osmond and Smythies[18] to suggest interference with the epinephrine cycle to explain the psychotomimetic effect. "It is particularly noteworthy that not only

LSD and mescaline but ergotropic agents in general, including amphetamine and ephedrine, when given in sufficiently large doses, induce aberrant behavior and illusions in man. This suggests that the reversible psychoses produced by these agents are an inevitable response of a highly tuned ergotropic system."[10]

PSYCHOTOMIMETIC EFFECTS

Medical interest in mescaline and LSD stems from a desire to understand the modus operandi of the psychotomimetic effect. As expressed by Cholden,[19] "the key to understanding psychiatry's deepest mystery, schizophrenia, might lie in the production of an experimental, predictable, controllable, reproducible state—an artificial psychosis."

States Simulating Psychosis

The psychotic phenomena produced by both mescaline and LSD are similar to the functional psychoses, a schizophrenic-like period of short duration characteristically associated with hallucinations, delusions, illusions, feelings of depersonalization, mood changes and catatonic signs.[2] Unique to LSD is its extreme potency, 3,000-5,000 times as much mescaline being required to effect similar psychic phenomena.[20]

Visual hallucinations, seen more commonly with mescaline, appear largely in the form of geometrical patterns or figures.[17] An interesting phenomenon is the occurrence of synesthesia—the stimulation of one sense perceived as a different sense; *i.e.,* sound producing a color sensation.[3] Colors are frequently vivid. Distortion of body image is common with the subject often feeling a sense of unreality or depersonalization.

Emotional changes may be related to previous personality—paranoid, euphoric, autistic and depressed reactions have all been encountered following administration of these drugs. Although the level of consciousness is unimpaired, time sense is frequently distorted.[3]

Some Effects On Intellectual Function

In an attempt to investigate their effects on the highest integrative functions, LSD and mescaline were administered to four artists and a writer whose integrative functions were impaired by the drug. In the artists' drawings color and line became boldly free and an unusual expansiveness and relaxation of control was apparent in their work.[21] In another study, Silverstein and Klee[22] found that the impairment of abstract thinking in normal subjects under LSD, as measured by the Gorham Proverbs Test, was similar to the relationship of scores obtained in testing normal and schizophrenic patients.

Experimental Studies On Spiders

To investigate the actions of these drugs, experiments have also been performed on various species of insect and animal life. A difference in the sites of action of LSD and mescaline is suggested by

the results of Witt's[23] experiments on spiders. Contrary effects on web construction were elicited from spiders following the administration of each of these compounds. As illustrated in the accompanying figures, LSD improves exactitude in the regularity and angles of web construction, while mescaline decreases the accuracy and urge to construct webs.[23]

(a) Marked exactitude of web produced with LSD. *(b) Erratic-type web produced by mescaline.*

Fig. 4. Changes in web construction following administration of psychotomimetic drugs to spiders.*

*Based on observations by Witt, P. N.[23]

Other Considerations of Symptomatology

Hoch[24] suggests that psychic integration becomes disorganized under the influence of LSD and mescaline, more so in the schizophrenic than the normal person. Resultant symptomatology has been reported to persist 24 hours in most cases.[25] Although Malitz[3] notes the absence of prolonged psychotic phenomena after these drugs, Elkes and associates[26] report serious after-effects lasting several days in some patients on LSD.

Forrer and Goldner[27] report intense euphoric outbursts following the administration of LSD to schizophrenic patients, as well as a greater accessibility to delusional material. Reactions in schizophrenics are more intense than in normals; the more pronounced symptomatology following mescaline may be attributable to its mode of administration.[17]

THEORIES OF PSYCHOTOGENIC ACTION

After observing the clinical and pharmacological effects of mescaline and lysergic acid diethylamide, different investigators have proposed several theories to explain their psychotomimetic action.

Interference with Epinephrine Cycle

Rinkel[28] believes that LSD and mescaline act by interfering with major enzyme systems, and possibly by involving the epinephrine cycle. He theorized that a noxious epinephrine metabolite is formed which may be the cause of the observed symptomatology.[2] This concept has been expanded by some workers to include the clinical psychoses which, it is postulated, might result from the development of an endogenous metabolite of epinephrine. Adrenochrome and possibly other degradation products of epinephrine have been suggested for this role;[5] this, however, has not been confirmed.

Competitive Inhibition of Neurohumors

Serotonin (5-hydroxytryptamine), a subject of the previous monograph in this series, is present in the brain and considered to be a mediator of the nervous system. *In vitro* LSD and related compounds are powerful inhibitors of serotonin. By competing for the same cell receptors, these psychotogenic antimetabolites of serotonin may block its physiological action.[2] Interference with the brain neurohumors has been suggested as a possible explanation for the psychiatric effects of this compound.[6,29]

However, Cerletti and Rothlin[30] do not accept this explanation, reporting that 2-brom-d-lysergic acid diethylamide (BOL 148), also a potent inhibitor of serotonin *in vitro,* has not produced abnormal symptoms in humans. Jarvik[6] suggests that one must consider the possibility of selective passage of certain substances through the blood-brain barrier. In the light of this discussion, it is well to call attention to the presence of the indole-like structure in mescaline, LSD and other psychotomimetics, such as hashish, ibogaine and harmine.[5] A similar nucleus is evident in serotonin.

Inhibition of Synaptic Transmission

Marrazzi[31] proposed a chemophysiological theory for the action of these compounds, with his demonstration of their inhibition of synaptic transmission. Conceivably, mental illness could represent abnormal patterns which have been released from normal restraining influences by inhibition of the higher centers. Thus, hallucinations may actually be stimulatory phenomena due to "release from normal restraining influences."[32] It has been suggested that LSD has a differential action, inhibiting the axodendritic and facilitating the axosomatic transmission.[33]

Function	Schizophrenia	LSD	Mescaline
Excretion	—	Feces	Urine
Cerebral respiration	Unaffected	Unaffected	—
Blood succinic and pyruvic acids	Accumulates	Accumulates	—
Epinephrine in blood	Lowered	Lowered	—
Hexosemonophosphate in blood	Accumulates	Accumulates	Unchanged
Liver function (Quick's test)	Disturbed	Disturbed	Disturbed
Serotonin excretion	Unchanged	Lowered	—
Inorganic phosphate excretion rate	Lowered	Lowered	—
Web construction by spiders	—	Improved	Lowered

Fig. 5. Some findings with LSD and mescaline compared with schizophrenia.* *Adapted from Lajtha, A.[8]

THERAPEUTIC APPLICATION OF MESCALINE AND LSD

The psychotomimetic drugs, originally employed as experimental tools, have also been helpful therapeutically in accelerating psychoanalytic therapy.[34] Savage[35] believes that LSD may liberate highly significant unconscious material by overcoming the patient's resistance. Frederking[36] and others have reported therapeutic gains through the psychocatharsis induced by these drugs; it is believed that they offer greater access to certain types of patients. Although LSD appears to have a wider spectrum of application, mescaline is preferred when the most intense emotional upheaval is sought.[36]

According to Lewis and Sloane,[37] the use of LSD in psychotherapy is "potentially valuable," although it "might seem to raise almost as many problems as it solves...." Hoch[38] believes LSD and mescaline offer information as to psychodynamics—ego strength, ego defenses, emotional regulation—but are not therapeutically beneficial to the patient. Tranquilizers, in reducing rather than aggravating symptomatology, are far better therapeutic tools than LSD and mescaline, although the latter are invaluable for therapeutic understanding. Additional work is needed to define and evaluate the therapeutic status of these compounds.[2]

THE FUTURE OUTLOOK

Although our present knowledge from experimental data still does not permit an adequate explanation of drug-produced psychoses, the psychotomimetic drugs continue to be utilized as an "experimental tool" in psychiatry.[8] Investigators are studying and attempting to correlate the neurophysiological and biochemical actions of these drugs with their mental effects.[2] Other similar-acting compounds must be studied to establish valid relationships.[8]

An additional application of the psychotomimetic drugs is the observation of the antidotal effect of various drugs in preventing or modifying artificially induced psychoses. The use of an intravenous phenothiazine, for instance, has proved effective in diminishing depersonalization and hallucinatory phenomena.[3] Evaluations of these and other experimental results are contributing to the painstaking

progress in the understanding of metabolic, neurophysiological and neuropharmacological changes that may be involved in the naturally occurring psychoses. These studies are adding new compounds to our armamentarium of drugs for the treatment of mental disease and its symptomatology. Together with the results of these and future investigative efforts, the psychotomimetic drugs may help us arrive at a more precise understanding of psychosis.

Bibliography: (1) Hoagland, H.: Ann. New York Acad. Sc. *66*:445, 1957. (2) Denber, H. C. B.; Rinkel, M., *et al.:* J. Nerv. & Ment. Dis. *125*:423, 1957. (3) Malitz, S.: New York J. Med. *57*:3293, 1957. (4) Overholser, W., in Kline, N. S.: Psychopharmacology, Washington, D. C., American Association for the Advancement of Science, No. 42, 1956, p. iii. (5) Hoffer, A.; Osmond, H., and Smythies, J.: J. Ment. Sc. *100*:29, 1954. (6) Jarvik, M. E., in Kline, N. S.: Psychopharmacology, Washington, D. C., American Association for the Advancement of Science, No. 42, 1956, p. 145. (7) Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, ed. 2, New York, The Macmillan Company, 1956, p. 889. (8) Lajtha, A., in Pennes, H. H.: Psychopharmacology, New York, Harper & Brothers, 1958, p. 126. (9) Hess, W. R., cited in Brodie, B. B.; Prockop, D. J., and Shore, P. A.: Postgrad. Med. *24*:296, 1958. (10) Brodie, B. B.; Prockop, D. J., and Shore, P. A.: Postgrad. Med. *24*:296, 1958. (11) Rothlin, E.: Ann. New York Acad. Sc. *66*:668, 1957. (12) Abramson, H. A.; Jarvik, M. E.; Gorin, M. H., and Hirsch, M. W.: J. Psychol. *41*:81, 1956. (13) Isbell, H.; Fraser, H. F.; Wikler, A., and Belleville, R. E.: abstracted, Fed. Proc. *14*:354, 1955. (14) Savage, C.: Psychoanalyt. Rev. *42*:1, 1955. (15) Goodman, L. S., and Gilman, A.: *op. cit.*, p. 175. (16) Hosko, M. J., and Tislow, R.: Fed. Proc. *15*:440, 1956. (17) Hoch, P. H.; Cattell, J. P., and Pennes, H. H.: Am. J. Psychiat. *108*:579, 1952. (18) Osmond, H., and Smythies, J.: J. Ment. Sc. *98*:309, 1952. (19) Cholden, L.: Lysergic Acid Diethylamide and Mescaline in Experimental Psychiatry, New York, Grune & Stratton, 1956, p. ix. (20) Rothlin, E.: J. Pharm. & Pharmacol. *9*:569, 1957. (21) Berlin, L., *et al.:* J. Nerv. & Ment. Dis. *122*:487, 1955. (22) Silverstein, A. B., and Klee, G. D.: A.M.A. Arch. Neurol. & Psychiat. *80*:477, 1958. (23) Witt, P. N.: Experientia *7*:310, 1951. (24) Hoch, P. H.: Am. J. Psychiat. *111*:787, 1955. (25) Becker, A. M.: Wien. Ztschr. Nervenh. *2*:402, 1949. (26) Elkes, C.; Elkes, J., and Mayer-Gross, W.: Lancet *1*:719, 1955. (27) Forrer, G. R., and Goldner, R. D.: A.M.A. Arch. Neurol. & Psychiat. *65*:581, 1951. (28) Rinkel, M., in Malitz, S.: New York J. Med. *57*:3293, 1957. (29) Richards, N.; Chapman, L. F.; Goodell, H., and Wolff, H. G.: Ann. Int. Med. *48*:1078, 1958. (30) Cerletti, A., and Rothlin, E.: Nature, London *176*:785, 1955. (31) Marrazzi, A. S.: Ann. New York Acad. Sc. *66*:496, 1957. (32) Marrazzi, A. S., cited in Denber, H. C. B.; Rinkel, M., *et al.:* J. Nerv. & Ment. Dis. *125*:423, 1957. (33) Purpura, D. P., cited in Rothlin, E.: J. Pharm. & Pharmacol. *9*:569, 1957. (34) Deniker, P.: J. Nerv. & Ment. Dis. *125*:427, 1957. (35) Savage, C.: J. Nerv. & Ment. Dis. *125*:434, 1957. (36) Frederking, W.: J. Nerv. & Ment. Dis. *121*:262, 1955. (37) Lewis, D. L., and Sloane, R. B.: J. Clin. & Exper. Psychopath. *19*:19, 1958. (38) Hoch, P. H.: J. Nerv. & Ment. Dis. *125*:442, 1957.

status of chemical and biological tests in psychiatric diagnosis

3

BACKGROUND

Symptomatic relief by chemical agents has rekindled interest in the possible use of biochemical changes in tests for mental illness.[1] In psychiatry the diagnostic classification of the mentally ill has depended largely upon the elucidation and delineation of certain symptoms and signs.

Various investigators have noted the need for better recognition as well as more accurate differentiation of the psychoses. Bleuler, discussing "schizophrenia" 40 years after his father had introduced the term, stated "We have no evidence of any disturbance which would neatly differentiate it from other psychoses, somatic disorders, or the norm."[2] More recently, in commenting on "...the recognized fallibility of psychiatric diagnosis," Meduna[3] stated that a laboratory test could be a most useful adjunct to clinical diagnosis.

The association of chemistry with psychiatric symptomatology is not new. Freud and Jung both had suggested a biochemical relationship to mental illness. The solution of pellagra and paresis by biological techniques[4] and, more recently, the recognition of a chemical basis for phenylpyruvic oligophrenia,[5] have given impetus to the search for biological and chemical correlates of mental illness.

This current review is devoted to an appraisal of certain experimental biological and chemical findings in mental illness and, more specifically, to their possible future application in psychiatric diagnosis. Since chemical changes may frequently be the result of mental illness rather than its cause,[4] mention will also be made in some instances of the significance of these changes in the etiology of psychoses.

INTRODUCTION TO BIOCHEMICAL TESTS

If, as Saunders[6] states, "the brain...is primarily a chemical organ" then some of the metabolites associated with brain function should lend themselves to recognition and quantitation. Investigational studies have revealed certain metabolic differences between psychotic and normal individuals and some of these may eventually be utilized as specific tests.

Knowledge of the progression of chemical reactions in psychic processes is still scant. Therefore, some of the following tests, although differing in the qualitative or quantitative changes studied, may actually show different stages in the same biochemical process. Thus, from the standpoint of psychiatric research, these tests should be viewed collectively as well as individually.

CATECHOLAMINES IN PSYCHIATRIC DIAGNOSIS

The general significance of the catecholamines, epinephrine and norepinephrine, has been discussed previously in this series and will not be reviewed here. Qualitative and quantitative studies have centered in large part on these catecholamines and amine metabolism in general, since it is in this

area that metabolic differences are often found in schizophrenia.[6,7] As indicative of their role in psychiatric symptomatology, Hoffer[8] states that catecholamines are clearly related to anxiety and mood. Similarly, Heath,[9] considering psychodynamic of secondary importance to biochemical factors, points out that, "The total outpouring of amines is much greater in schizophrenics than in nonpsychotics. . . ."[10]

Norepinephrine and epinephrine have been quantitated in cerebrospinal fluid as well as in the plasma of normal and psychiatric individuals.[11] The observed changes appear to have diagnostic applicability; their validity and significance have yet to be established.

URINARY INDOLES IN MENTAL DIAGNOSIS

The potential role of the indole nucleus in psychotic symptomatology has been mentioned in an earlier review. The possibility of its application as a chemical test is based on the observation that the indole content of schizophrenic urine differs from normal urine.[12,13] So many urinary indoles are present, however, that findings are difficult to interpret.[2] If the search is limited to indoles derived from tryptophane or epinephrine, the problem is lessened.[14]

Leyton[15] has compared the indoles found in schizophrenic and normal urines. Each indole made a "spot" on specially treated paper, the density of which was proportional to the amount of indole present. The table below summarizes his findings:

COMPARISON OF URINARY INDOLES IN SCHIZOPHRENICS AND CONTROLS*

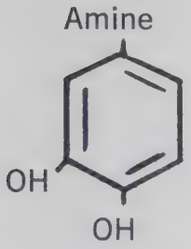
Indolic Compound	Maximal Density of Spots	
	Schizophrenic Urine	Normal Urine
Spot S	22.0	9.5
Spot Q	29.0	19.1
5-Hydroxy-indolyl acetic acid	22.9	26.7
Tryptophane	28.9	30.4
Indolyl acetic acid	25.7	24.3
Indolyl acetyl glutamine	28.1	30.0
Potassium indoxyl sulphate	27.6	29.6

*Adapted from Leyton, G. B.[15]

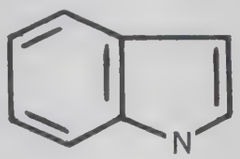
Only 5 of the substances are known beyond reasonable doubt; for want of identification the remaining indolic compounds are referred to as Spot Q and Spot S. Of the 7 indolic substances excreted, "...the difference in depths of Spots S and Q between schizophrenics and controls may be of some assistance in the diagnosis of early or obscure cases of schizophrenia."[15] The difference in 5-hydroxy-indolyl acetic acid, while apparently not suitable as a specific test for schizophrenia, offers the possibility of a biochemical classification of schizophrenias since it is shown by only 20% of these

patients. This might be "...particularly valuable if it were found possible to correlate this biochemical abnormality with other differences in symptoms and prognosis."[15]

Two basic nuclei of significance in brain chemistry



CATECHOLAMINE



INDOLE

CERULOPLASMIN—SIGNIFICANCE IN DIAGNOSIS

One of the first explorations into the possibility of chemical tests for mental illness was done by Stig Akerfeldt, a Swedish investigator.[16] He observed that blood serum from mentally ill patients, including schizophrenics, manic-depressives and senile psychotics, had a specific oxidative property lacking in normal subjects. When he added DPP (N,N-dimethyl-p-phenylenediamine) to the serum of these patients he obtained a red reaction. It was postulated that this catalytic oxidation is related to the more active and higher ceruloplasmin concentration and the lower ascorbic acid concentration in schizophrenic serum.[17]

Characteristics of Ceruloplasmin

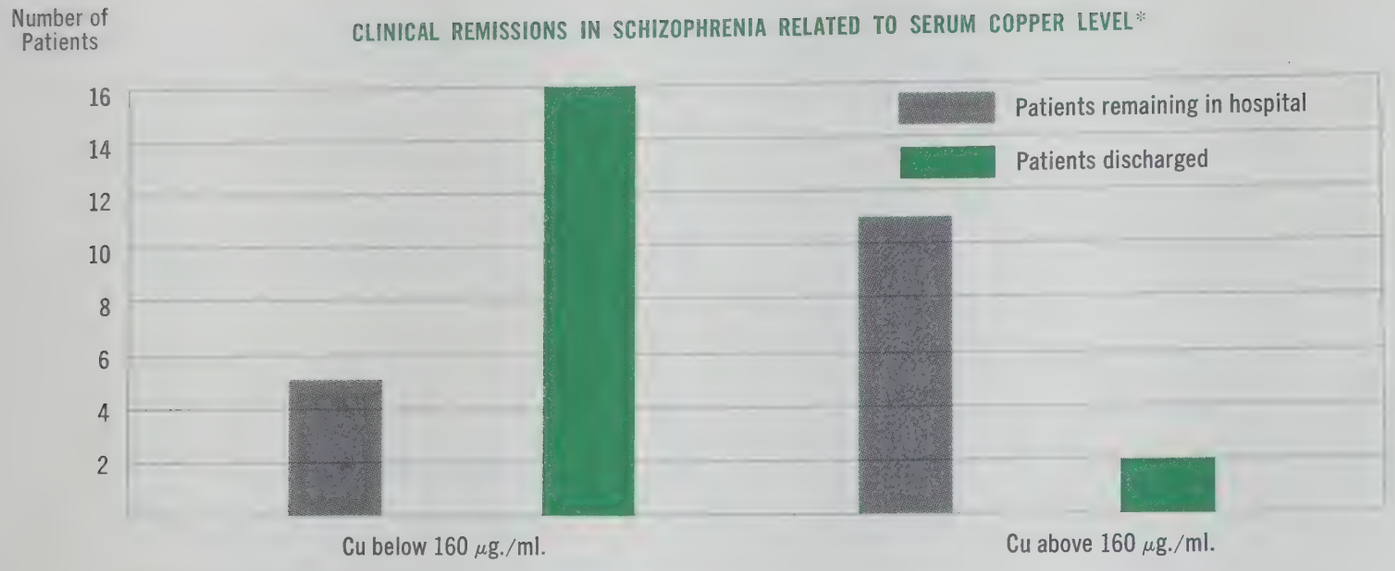
Ceruloplasmin is a copper alpha globulin compound; since it contains approximately 95 per cent of the serum copper, the concentration is a reliable indicator of the amount of ceruloplasmin present.[9] *In vitro,* at least, ceruloplasmin is an oxidase[9,17] which is believed to be essential to amine metabolism in man.[9] It is interesting to note that Saunders[18] reports increased copper in the plasma of patients under phenothiazine therapy.

Clinical Status of the Test

Heath[9] proposes "...that the ceruloplasmin response might be an important part of the mechanism for counteracting the psychotic process." He reports a correlation between the level of ceruloplasmin and the remission rate in 34 hospitalized schizophrenics. Another group of investigators[19] measured serum ceruloplasmin levels in 26 consecutive clinic patients and found that the increased ceruloplasmin levels in the disturbed group were "...evident and...significant."

Evaluation of Ceruloplasmin

Although many enthusiastically hailed this advance, Akerfeldt himself had pointed out the lack of specificity, since this test was also positive in liver disease, cancer, rheumatoid arthritis and pregnancy.[17] Frohman *et al.*[12] point out that other compounds may play a part in the enzymatic process. According to another investigator,[17] the lack of consistency in reports "...indicates a need for a



*Adapted from Heath, R. G., et al.[9]

more critical assessment...." At present, most investigators feel that the serum ceruloplasmin level is not a useful diagnostic aid in psychiatry.[17]

TARAXEIN—A QUALITATIVE TEST?

Studies with ceruloplasmin led to the discovery of taraxein,[2] an unknown psychotomimetic substance reputedly found in schizophrenic serum. Following intravenous administration in monkeys of one of the globulin fractions obtained from the serum of schizophrenic patients, the changes recorded on subcortical electrodes were seen to resemble those observed in schizophrenics. Symptoms typical of endogenous schizophrenia were then observed when the same fraction was administered to volunteers.

The nature of taraxein is not well known. It is unstable, difficult to isolate and hard to preserve in activity. "The substance is, however, unquestionably a protein [a globulin] and of large molecular size...."[20]

Comparison Study

The test dose of taraxein which was injected into a normal person was the amount extracted from 400 cc. of schizophrenic serum. Control injections of normal serum, similarly processed, failed to produce psychotic symptoms in normal volunteers.[20] This step was taken since the likelihood existed that the processing procedure may have activated a precursor in schizophrenic serum. From these observations it appeared that taraxein was a psychotomimetic substance obtained from schizophrenic serum.

Theory of Action

Heath[9] is of the opinion that "...taraxein represents a difference or defect in the oxidizing enzyme system. This oxidizing enzyme system, including ceruloplasmin and taraxein...has acted on epinephrine and related substances." Taraxein may interfere with catecholamine oxidation causing the formation of a toxic substance which induces psychotic behavior by altering brain physiology.[9,20]

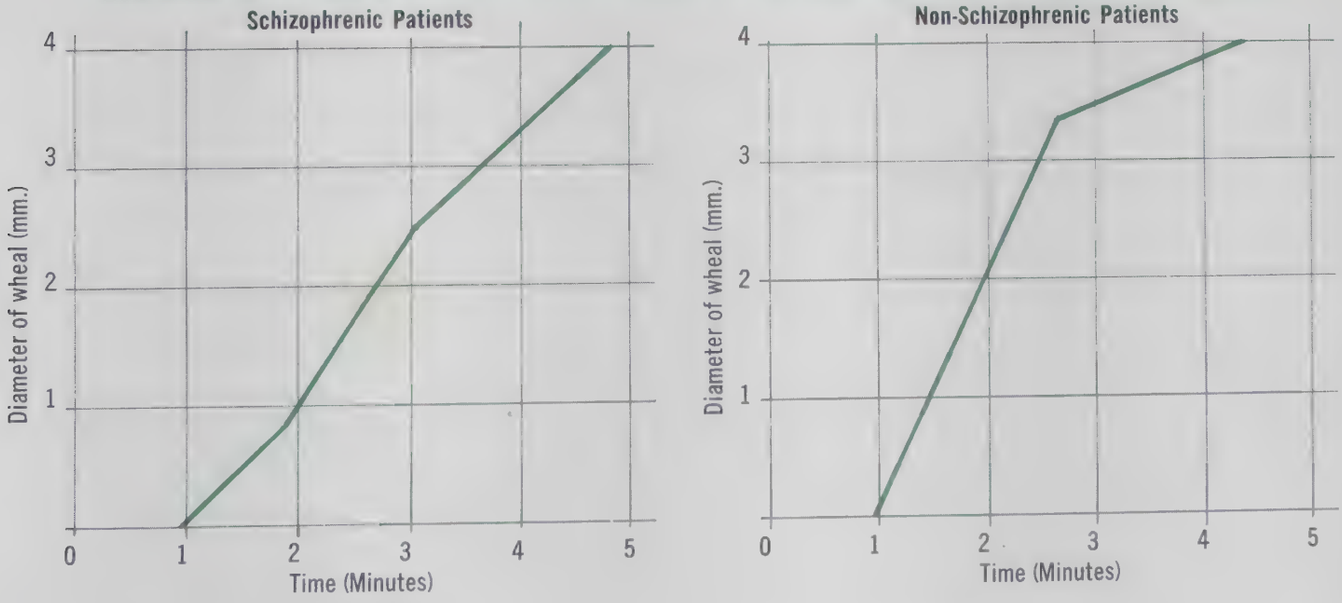
Criticism

Siegel *et al.*[21] call attention to the dearth of confirmatory evidence. In seven "meticulous attempts"[21] they were unable to obtain confirmation of Heath's findings. This group[21] considers taraxein at present, "...a hypothetical substance." Martens, working with Melander,[22] as well as Russian investigators, working independently, have reported confirmation of Heath's work. Currently there is considerable controversy as to the significance of the findings of Heath and his group, and the status of taraxein in diagnosis is questionable.

THE HISTAMINE TEST IN PSYCHIATRY

Gooszen and Donker[23] indicate a relationship between histamine and mental illness. Allergic responses are reportedly less frequent in psychotic individuals.[24,25] Weckowicz and Hall[25] reported in 1957 "a skin histamine test which differentiates between schizophrenics and non-schizophrenics...," the former showing "delayed and weaker skin reaction to intradermal application of histamine."

COMPARISON OF TWO GROUPS SHOWING DELAYED RESPONSE TO HISTAMINE INJECTION IN SCHIZOPHRENIC PATIENTS*



*Adapted from Weckowicz, T. E., and Hall, R.[25]

Test and Technique

In the described test,[25] a drop of 1:1000 solution of histamine base is applied to the vaccination area of the arm followed by a stabbing puncture through the area made with a vaccination needle. The size of the wheal is measured at one-minute intervals for five minutes. Beside the size of the wheal, the other important factor is its speed of formation.

Jodrey and Smith[26] studied the histamine skin reaction in 291 mental patients and 51 normal subjects, and analyzed the data for the effect of certain variables, such as drug treatment, diagnosis, length of hospitalization, etc. They found that normal individuals and patients off medication reacted similarly to injected histamine; drugs apparently increased the tolerance to histamine. In view of the differences of technique and evaluation of the test in the two reports, the need for more studies is evident.

OTHER METABOLIC CHANGES AS POSSIBLE TESTS

Although glutathione levels have been reported to be lowered in schizophrenics,[6] it is not a change specific for schizophrenia.[27] Some investigators[28] have not confirmed a statistically significant difference between the reduced glutathione (GSH) levels of schizophrenics and normals.

Bogoch[29] has reported the mean neuraminic acid content of cerebrospinal fluid in schizophrenics as considerably below normal. The significance of this in diagnosis is still unknown and requires further study.

BIOCHEMICAL ASSAY AS A TEST

Hoffer and Osmond,[14] reasoning from their adrenochrome-adrenolutin theory of psychosis (discussed in a previous review), suggested that differences would be found between the body fluids of

EFFECTS OF NORMAL AND SCHIZOPHRENIC PLASMA ON BIOLOGIC PHENOMENA*

	Toxic Effects	
Biologic Phenomenon	Normal Plasma	Schizophrenic Plasma
Rat-climbing test	None	Yes
Spore germination	None	Yes
Spider web	None	Yes
L strain fibroblasts	None	Yes
Catatonia in pigeons	None	Yes

*Adapted from Hoffer, A., and Osmond, H.[14]

schizophrenics and normals. Accordingly, these investigators examined the effect of these fluids in biological assays, as listed in the table on the preceding page. Rat-climbing test, spore germination, spider-web formation, the effect on cell growth (L strain fibroblasts), and the catatonizing effect on pigeons were all tested. Results indicate the differences elicited; Hoffer and Osmond[14] conclude that these differences now offer the possibility of discriminating "...between schizophrenic groups and others...."

RESPONSE TO PSYCHOTOMIMETICS

Mentioned in an earlier review as being of diagnostic value in psychiatry, is the response to psychotomimetics. Jost[30] and Pemsl report the recognition of masked (unclear or latent) schizophrenic or manic-depressive states by the accentuation of symptoms after administration of mescaline or LSD. Manger *et al.*[11] state that the increase of epinephrine-like substance in four patients with mental illness after mescaline was administered "...suggests that a difference may exist between the physiochemical responsiveness of some psychiatric patients and normal subjects."

EVALUATION AND CONCLUSION

The value of these tests at present lies in their contribution to basic psychiatric research as well as to their possible future role in psychiatric diagnosis. Although "there are few short cuts to the acquisition of knowledge,"[17] many clues to brain function may be obtained from these tests.

As stated by Hoffer and Osmond,[14] thousands of patients should be studied by similar tests before these may be accepted as scientifically valid. Kline[31] points out several factors that limit the value of these laboratory findings; these are the as yet uncontrolled variables—such as diet, age, sex, infection and psychological factors. Ultimately we can expect that continued investigations will help in the designation of an enzyme or product that is present or absent to the degree we call pathology.[32]

Bibliography: (1) Cafruny, E. J., and Domino, E. F.: A.M.A. Arch. Neurol. & Psychiat. *79*:336, 1958. (2) Osmond, H., and Hoffer, A.: Canad. M.A.J. *80*:91, 1959. (3) Meduna, L. J., in Blood Tests in Mental Illness, Ann. Conf. Brain Res. Found., Chicago, Jan. 12, 1957, p. 44. (4) Kety, S. S.: Ann. New York Acad. Sc. *66*:836, 1957. (5) Pauling, L. C.: Mod. Med. *27*:226, 1959. (6) Saunders, J. C., in Dorfman, W.: Some Chemical Concepts in Psychosomatic Medicine, Tr. 5th Ann. Meet. Acad. Psychosom. Med., 1958, p. 103. (7) Hoagland, H.: Ann. New York Acad. Sc. *66*:445, 1957. (8) Hoffer, A.: The Relationship of Iproniazide to Epinephrine Metabolism, presented at Conf. on Amine Oxidase Inhibitors, New York Acad. Sc., Nov. 20-22, 1958. (9) Heath, R. G., *et al.*: Am. J. Psychiat. *114*:683, 1958. (10) Heath, R. G., in Rinkel, M., and Denber, H. C. B.: Chemical Concepts of Psychoses, New York, McDowell Obolensky, 1958, p. 432. (11) Manger, W. M., *et al.*, in Dorfman, W.: Tr. 5th

Ann. Meet. Acad. Psychosom. Med., 1958, p. 52. (12) Frohman, C. E., *et al.:* A.M.A. Arch. Neurol. & Psychiat. *79*:730, 1958. (13) McGreer, P. L.; McGreer, E. G., and Gibson, W. C.: Science *123*:1029, 1956. (14) Hoffer, A., and Osmond, H.: J. Nerv. & Ment. Dis. *128*:18, 1959. (15) Leyton, G. B.: Brit. M. J. *2*:1136, 1958. (16) Akerfeldt, S.: Science *125*:3238, 1957. (17) McDonald, R. K., in Rinkel, M., and Denber, H. C. B.: Chemical Concepts of Psychoses, New York, McDowell Obolensky, 1958, p. 230. (18) Saunders, J. C., in Kline, N. S.: Psychopharmacology Frontiers, Boston, Little, Brown & Company, 1959, p. 410. (19) Ostfeld, A. M.; Abood, L. G., and Marcus, D. A.: A.M.A. Arch. Neurol. & Psychiat. *79*:317, 1958. (20) Heath, R. G., *et al.,* in Rinkel, M., and Denber, H. C. B.: Chemical Concepts of Psychoses, New York, McDowell Obolensky, 1958, p. 223. (21) Siegel, M., *et al.:* Am. J. Psychiat. *115*:819, 1959. (22) Melander, S., and Martens, S.: Dis. Nerv. System *19*:478, 1958. (23) Gooszen, J. A. H., and Donker, J.: Acta allergol. *10*:149, 1956. (24) Coca, A. F.; Walzer, M., and Thomen, A. A.: Asthma and Hay Fever in Theory and Practice, Springfield, Ill., Charles C Thomas, 1931. (25) Weckowicz, T. E., and Hall, R.: J. Nerv. & Ment. Dis. *125*:452, 1957. (26) Jodrey, L. H., and Smith, J. A.: Am. J. Psychiat. *115*:801, 1959. (27) Martens, S., *et al.:* A.M.A. Arch. Neurol. & Psychiat. *76*:630, 1956. (28) Barak, A. J.; Humoller, F. L., and Stevens, J. D.: A.M.A. Arch. Neurol. & Psychiat. *80*:237, 1958. (29) Bogoch, S.: A.M.A. Arch. Neurol. & Psychiat. *80*:221, 1958. (30) Jost, F., and Pemsl, H.: München. med. Wchnschr. *99*:889, 1957. (31) Kline, N. S., in Rinkel, M., and Denber, H. C. B.: Chemical Concepts of Psychoses, New York, McDowell Obolensky, 1958, p. 401. (32) Kline, N. S.: Psychopharmacology Frontiers, Boston, Little, Brown & Company, 1959, p. 17.

4

THE RETICULAR ACTIVATING SYSTEM

This study is the first in the current series devoted exclusively to structure-function relationship, the basic discipline of neurophysiology. Specifically it attempts to survey our present state of knowledge of the reticular activating system, little known a dozen years ago but now acquiring increasing significance neurologically, psychiatrically and pharmacologically. If accepted, the new concepts of the function of the reticular system constitute a total revolution in theories of cortical integration.

BACKGROUND

When sensory pathways are interrupted at midbrain level, an experimental animal will nevertheless remain in as wakeful a state as the animal with its nervous system intact. In spite of the interruption of these sensory tracts, both auditory and somatic stimulation will arouse the sleeping animal; thus, "...stimuli *that the animal presumably cannot hear or feel*..."[1] have produced a wakeful state. Arousal by afferent stimuli, in the absence of the classical sensory fiber tract, is thought to be mediated by the reticular activating system (RAS).

In the not too distant past, neurophysiology attributed sensory analysis to discrete areas in the cortex which receives sensory "messages" by way of "long, direct, compact, lemniscal pathways...."[2] A revolution in neurophysiologic thinking was occasioned by the recognition of an extralemniscal pathway, the reticular activating system which, it is believed, can influence cortical centers.

A DEVELOPMENTAL VIEW

Students of neurology had explained function largely in terms of the reflex arc and of specialized higher centers receiving fixed fiber tracts. This organization of central nervous system function at *horizontal* levels was emphasized by studies of decorticate, decerebrate and spinal animals. It was the zoologist George Ellett Coghill who first deviated from neurologic orthodoxy in suggesting that function might be organized in a *vertical* manner as well.[3]

While studying the development of the salamander brain Coghill had identified a mass of small nerve cells interposed between sensory and motor components. To these functionally undifferentiated cells, the "neuropil," he attributed the development of sensory and motor patterns. Such individual patterns are apparently derived from repetitive experiences. Similarly, based on reiteration of

experiences, selective pathways are thought to develop in the nervous system of the growing amblystoma. This patterning takes place in an area somewhat analogous to the primitive "neuropil"—the reticular formation. Though incomplete, physiologic studies suggest that the brain stem reticular formation influences both sensory input and motor output.[3]

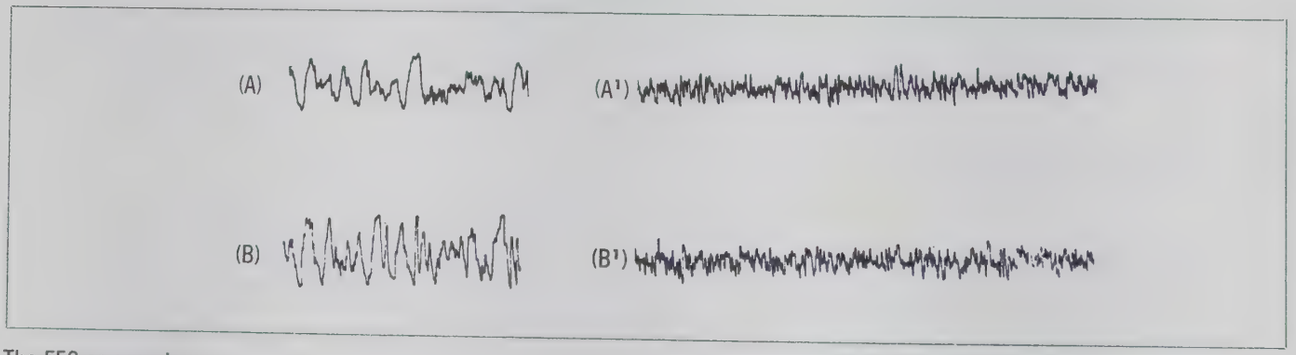
Evidence has related these reticular pathways to autonomic control, neuromuscular function and especially to subserving the attributes of "consciousness." This latter function underscores the role of the RAS in clinical psychiatry. As stated concisely by French:[4] "The reticular activating system . . . must be considered the great integrating mechanism of the brain without which unity of response to complex environmental stimuli is impossible." Stated simply, this system contains the basis of the conscious awareness which permits man to react appropriately to his environment.

THE AROUSAL REACTION AND THE RAS

Direct stimulation of the reticular formation of the animal brain stem produces EEG changes seemingly identical with those activating changes observed in the human EEG on awakening from sleep; there is a change from high-voltage slow waves to low-voltage fast waves. From this activation of the EEG, Himwich[5] states, the name, reticular (or mesodiencephalic) activating system, was derived.

In the cat this characteristic activation pattern, on stimulation of the reticular system, appears together with behavioral signs of alertness. Such an EEG is indistinguishable from that obtained from a human being upon opening of the eyes or upon hearing a sudden loud sound.[6] Recognition that this "arousal" reaction and the state of wakefulness are related to the ascending fibers of the RAS is due largely to the experimental observations of Magoun.[7]

FIG. 1*



The EEG as seen in

(A) sleeping monkey
(B) sleeping monkey with electrodes implanted in brain stem
(A¹) monkey awakening
(B¹) same monkey following brain stem stimulation

Note similarity of pattern in A¹ and B¹.

*Adapted from Magoun, H. W.[2]

ANATOMY

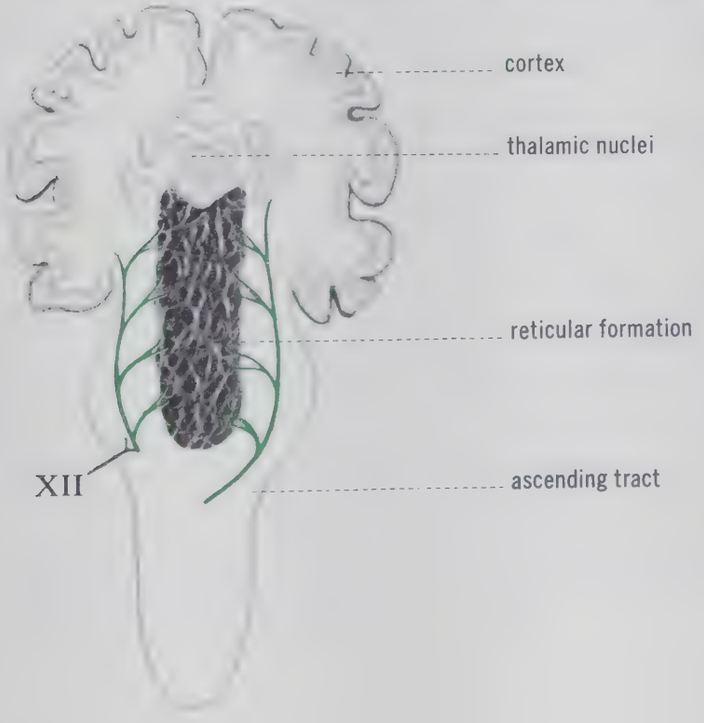
As with many other neuroanatomical structures, both physiologic and anatomic terms have been employed in defining this loose network (reticulum). The RAS is a medially located "internuncial" pathway, of diffuse input and output extending the entire length of the neuraxis.[3,8] Allen[9] states that the RAS is "...that mass of cells in the brain stem and spinal cord that is not utilized in the formation of motor-root or sensory-relay nuclei." Phylogenetically speaking, "...this brain stem reticular formation appears not so much... a completely new development as a rostral enlargement and specialization of interneuron collections...."[10]

This system extends through the bulb, pontine and mesencephalic areas; it includes also the functionally related subthalamus, hypothalamus and ventromedial portion of the thalamus. Anatomically and physiologically, a distinction is made between caudal (reticular) and rostral (thalamic) portions.

FIBER CONNECTIONS

This vital integrating system receives all afferent sensory paths,[11] receives and sends fibers to various parts of the cerebral cortex, the cerebellum, the hypothalamus and the internuncial pools at various levels. Histologically, notwithstanding the diffuse sensory input, one may observe the "...highly organized and potentially selective pathway for both motor and sensory conduction."[3] Ascending and descending tracts from the reticular system influence markedly central and peripheral neural activity subserving, "...on the one hand, behavioral facilitation and, on the other hand, the central alertness that characterizes the waking state."[7]

FIG. 2 DIAGRAMMATIC REPRESENTATION OF THE RETICULAR FORMATION*



*Adapted from French, J. D.[4]

functions and significance

Long recognized anatomically, the reticular formation is strikingly novel in its functional significance.[12] However, despite voluminous literature and the multiplicity of functions assigned to this system, the latter are theoretical and largely unproved. Functional roles have been attributed to the reticular formation in the waking state, in emotions and behavioral patterns, in learning, in neuromuscular function and in autonomic regulation. This considerable influence, "...which enables man to react appropriately in his environment," is presumably transmitted by ascending and descending fibers arising from within the reticular system.[4]

THE WAKING STATE

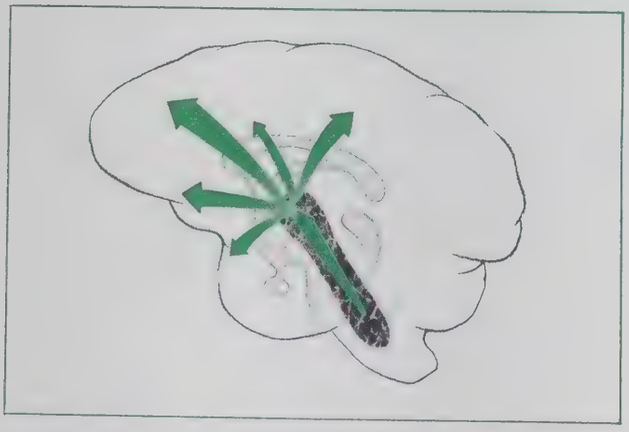
Functions generally accepted for the reticular system are *general arousal*—the transition from sleep to waking (previously described)—and *general alerting,* or attentiveness. *Specific alerting,* or focused attention, has been recognized behaviorally, but not experimentally.[13]

Relation of the RAS to consciousness is more difficult to establish. Consciousness has been defined as an "...awareness of environment and of self."[14] It is perhaps the alertness that characterizes the waking state, the level of "consciousness," which is affected over-all by the RAS.[1,10] This may be explained by the fact that all sensory stimuli reach the responsive RAS.[4] These ascending sensory impulses pass through the reticular system and evoke a widely spread "alerting" reaction over the cerebral cortex.

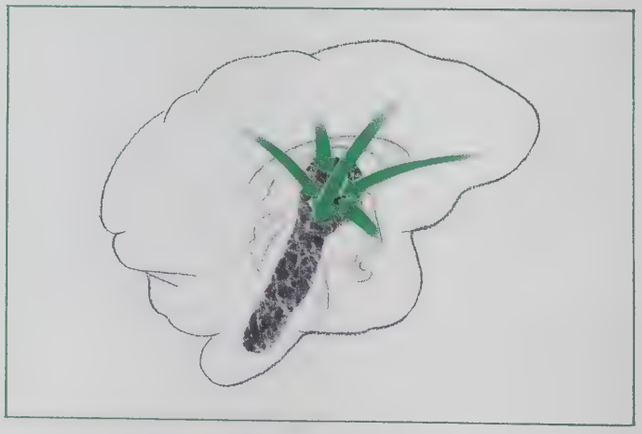
Investigations also suggest descending corticoreticular pathways arising from discrete cortical areas.[3,15] Through these the content and degree of consciousness may also be controlled by the cortex. This selective mechanism of conscious responsiveness may offer an acceptable neurophysiological explanation for the sleeping mother who awakens to her baby's cry but is oblivious to the roar of traffic.[1]

In terms of consciousness the RAS may also explain the action of certain anesthetics and certain forms of narcolepsy. Anesthetics, though acting diffusely, "...have a predilection for the reticular

FIG. 3 CONNECTIONS BETWEEN RETICULAR SYSTEM AND CEREBRAL CORTEX



Ascending Fibers to Cortex from RAS*
*Adapted from Magoun, H. W.[2]



Descending Fibers to RAS from Cortex*
*Adapted from Livingston, R. B.[15]

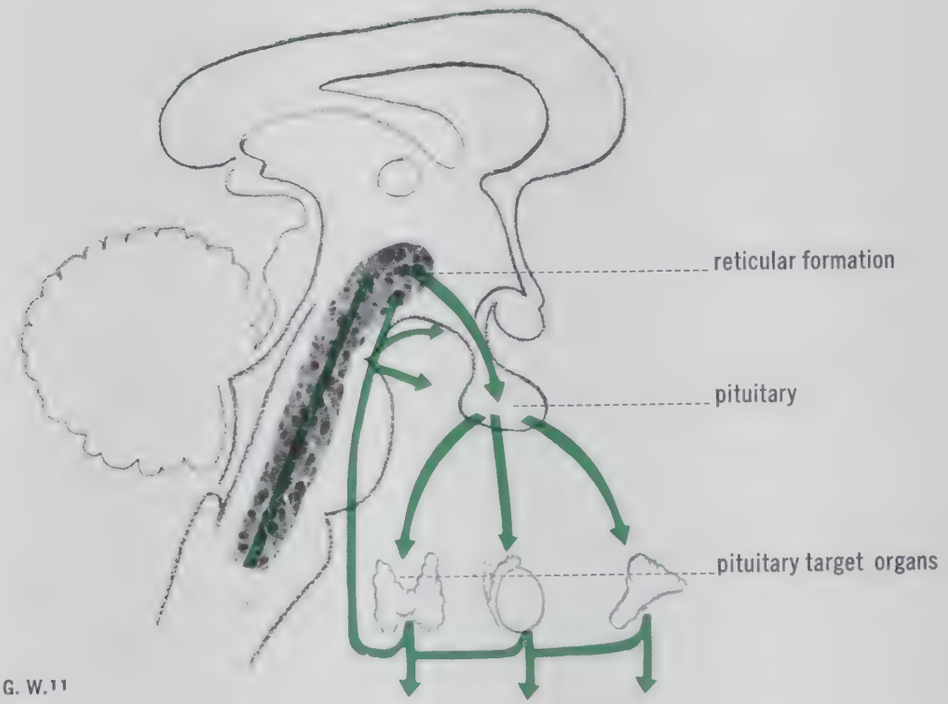
activating system. . . ."[16] Clinically, damage to the reticular formation has produced a sleep-like state.[16,17] Study of this system may thus eventually shed light on some of the mechanisms involved in certain regressive forms of human behavior.[3]

EMOTIONS AND BEHAVIORAL PATTERNS

The reticular system, together with the hypothalamus and limbic system, participates in the control of emotions.[11] Depression of this system removes a known source of hypothalamic excitement. Linn[1] has suggested that the cortex scans incoming impulses and "deactivates" the RAS (lessening the individual's awareness) when emotionally charged impulses are recognized, thereby reducing anxiety.

"Just as the reticular system may excite or inhibit the activity of the cerebral cortex and so result in changes of behavior . . ."[11] it also affects pituitary secretion; these changes in glandular function may cause behavioral changes. This is schematically represented in Fig. 4.

FIG. 4 SCHEMATIC ILLUSTRATION OF POSSIBLE RELATIONSHIPS OF THE RAS TO HORMONAL SECRETION VIA THE HYPOTHALAMOPITUITARY AND PITUITARY TARGET ORGANS (NOT ALL ARE SHOWN)*



*Adapted from Harris, G. W.[11]

In clinical psychiatry the implications of these relationships are great. In addition there is a marked susceptibility of this area to drugs[3] and to neurohumors[4] which emphasizes the therapeutic potential of psychochemical agents and the significance of this system.

THE LEARNING PROCESS

According to Penfield[18] the RAS integrates corticofugal impulses into memory patterns, thus relating this system to the learning process. Livingston, Haugen and Brookhart,[3] as mentioned previously, consider that repetitive impulses modify synaptic associations. Thereby, "learned" as well as "innate" patterns of neural organization are developed.

EFFECT ON MOTOR SYSTEM

Both reduction and augmentation of muscular activity have been attributed to areas in the reticular formation.[3] Abnormal reticular activity may be held accountable in some instances for hyperreflexia or for involuntary movement, as in tremor.[10] Spasticity has been induced experimentally in animals.[4] The hypokinetic state, as seen in some clinical syndromes, may be explained in part by lesions in the brain stem which produce a "reduction of background excitation within the cord. . . ."[10]

ROLE IN AUTONOMIC REGULATION

Cardiovascular, respiratory, metabolic, visceral and temperature-control centers coexist with the RAS in the brain stem. These are believed to be functionally inseparable from reticular activity.[4]

action of tranquilizers on reticular activating system

Evidence is still incomplete concerning the specific mode of action of the tranquilizers. Although phenothiazines and barbiturates both depress the RAS, there is marked difference in the mobile status produced in a patient by these classes of drugs. This difference between narcosis, sedation and tranquilization is attributed to dissimilar patterns of neurophysiologic action.[19]

In part, at least, tranquilization appears to be aided by depression of the reticular system, eliminating it as a source of emotional expression through the hypothalamus.[20] Animal experiments show these effects of drugs on the activity of the reticular system: (1) a diminution of sensitivity to sensory and harmful impulses and (2) a suppression of activation effects of circulating epinephrine.[21]

changing concepts in neurophysiology

STAGES IN NEUROLOGIC VIEW OF BEHAVIOR

From the historical point of view the neurologic explanation for man's behavior might be seen first as the *stage of self-action,* i.e., the mechanistic, simple-reflex concept of nervous action. In the next stage, the *stage of interaction,* compartmentalization occurs with higher centers dominating lower ones, all interacting by connecting fiber tracts.[3]

However, with recognition of the significance of the RAS, emphasis "...has shifted away from the long [fiber] tracts and the main nuclear masses..."[3] to what is often termed a *transactional view* of human behavior. This medially placed internuncial pathway (the RAS) has transformed the compartmentalized concept of specific function in specific structures which interact in a fixed manner to the dynamic concept of the nervous system wherein the stimulus-response involves the functional whole.[3]

FULFILLMENT OF A PROPHECY

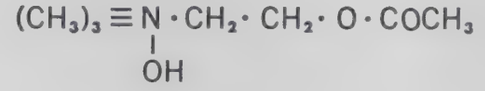
In 1897 Sherrington wrote: "The fibres passing down from the cortex to the mid-brain have probably functions by which they take part even in our psychical life, functions for which the words neither motor or sensory are fitting."[22] The supposition that cortical associations or interplay are sufficient to explain the integrated behavior of conscious man no longer appears tenable.[23] In continuing anatomic, physiologic and clinical exploration of the reticular activating system we may expect greater insight into the relationship of mind and brain, the behavioral integration of man and, thus, into the pathways of mental dysfunction.

Bibliography: (1) Linn, L.: Am. J. Psychiat. *110*:61, 1953. (2) Magoun, H. W., in Clinical Neurosurgery, Baltimore, Williams & Wilkins, 1957, p. 186. (3) Livingston, W. K.; Haugen, F. P., and Brookhart, J. M.: Neurology *4*:485, 1954. (4) French, J. D.: J. Neurosurg. *15*:97, 1958. (5) Himwich, H. E., and Rinaldi, F.: Yale J. Biol. & Med. *28*:308, 1955. (6) Maruzzi, G., and Magoun, H. W., cited by Glotfelty, J. S., and Wilson, W. P.: North Carolina M. J. *17*:401, 1956. (7) Magoun, H. W., cited by Linn, L.: Am. J. Psychiat. *110*:61, 1953. (8) Wikler, A.: The Relation of Psychiatry to Pharmacology, Baltimore, Williams & Wilkins, 1957, pp. 126, 132, 135. (9) Allen, W. F., cited by French, J. D.: J. Neurosurg. *15*:97, 1958. (10) Magoun, H. W.: Physiol. Rev. *30*:459, 1950. (11) Harris, G. W., in Jasper, H. H., *et al.*: Reticular Formation of the Brain, Boston, Little, Brown & Company, 1958, p. 207. (12) Nauta, W. J. H., and Kuypers, H. G. J. M., in Jasper, H. H., *et al.*: *ibid.*, p. 3. (13) Lindsley, D. B., in Jasper, H. H., *et al.*: *ibid.*, p. 513. (14) Cobb, S., in Feldberg, W.: Brit. M. J. *2*:771, 1959. (15) Livingston, R. B., in Clinical Neurosurgery, Baltimore, Williams & Wilkins, 1957, p. 192. (16) Feldberg, W.: Brit. M. J. *2*:771, 1959. (17) French, J. D., cited by St. Onge, K. R., and Calvert, J. J.: J. Speech & Hearing Disorders *24*:43, 1959. (18) Penfield, W., cited by Wikler, A.: The Relation of Psychiatry to Pharmacology, Baltimore, Williams & Wilkins, 1957, p. 133. (19) DeMaar, E. W. J.; Martin, W. R., and Unna, K. R.: J. Pharmacol. & Exper. Therap. *124*:17, 1958. (20) Himwich, H. E.; Rinaldi, F., and Willis, D.: J. Nerv. & Ment. Dis. *124*:53, 1956. (21) Courvoisier, S., cited by Glotfelty, J. S., and Wilson, W. P.: North Carolina M. J. *17*:401, 1956. (22) Jefferson, G., in Jasper, H. H., *et al.*: Reticular Formation of the Brain, Boston, Little, Brown & Company, 1958, p. 729. (23) Penfield, W., in Jasper, H. H.: *ibid.*, p. 739.

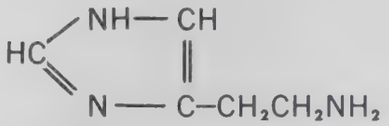
ACETYLCHOLINE AND HISTAMINE

At least four types of neurohumoral substances have a function in the nervous system: acetylcholine, sympathin, histamine and serotonin. These substances are interrelated both inside and outside the central nervous system and it is more than likely that they have some effect upon behavior. In the sphere of abnormal behavior they have been studied particularly in relation to schizophrenic disorders. Of significance is the fact that many agents that modify, inhibit or stimulate the action of these substances bring about profound changes in human behavior.[1] It is thought that acetylcholine and histamine may act as neurochemical transmitter substances but the evidence is thus far incomplete.[2]

ACETYLCHOLINE



HISTAMINE



5

ACETYLCHOLINE

Background

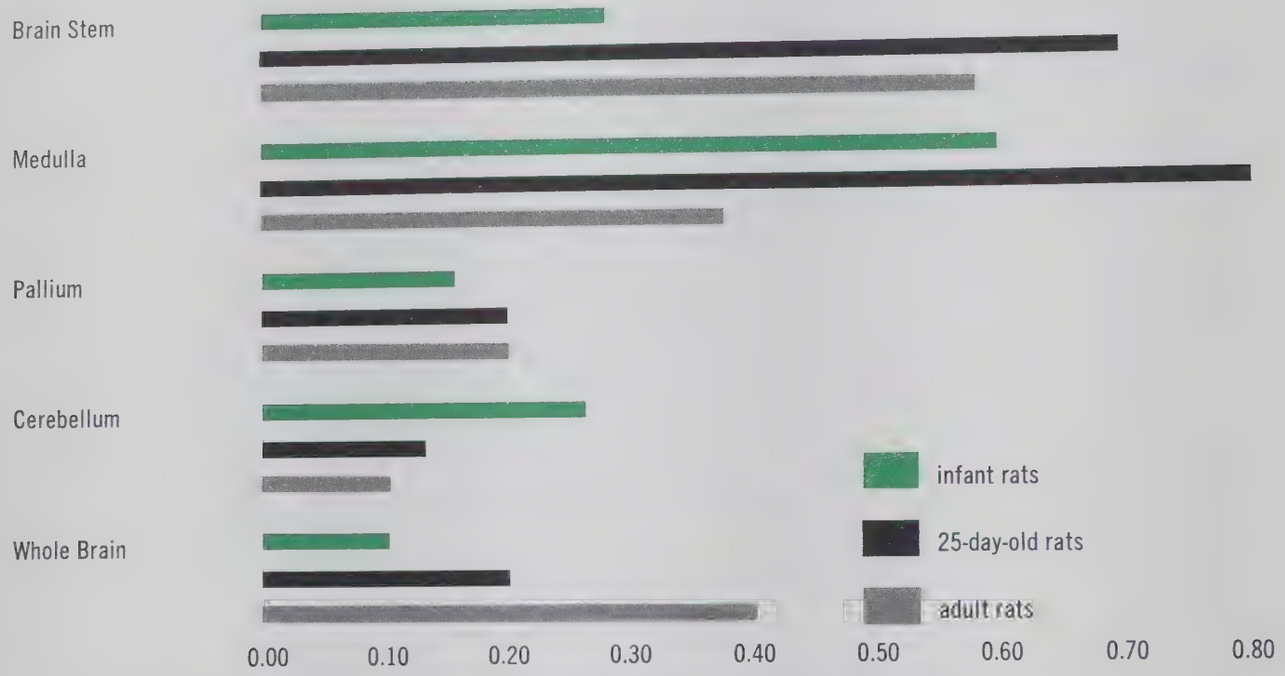
Although acetylcholine was synthesized as early as 1867, it was not until 1921 that the first direct evidence of its transmitter function was established.[1] Further investigations as to the distribution of cholinesterases and choline acetylase in the central nervous system have led to increased interest in the role of acetylcholine as a central transmitter.[2] Extensions of this work on synaptic transmission and on the effects of cholinergic substances have resulted in attempts to implicate acetylcholine in the neurochemical balance system involved in behavior.

Distribution and Metabolism in the Central Nervous System

In the mammalian central nervous system, the cerebellum contains the least acetylcholine of any part of the brain, and the brain stem, the most, according to Quastel.[3] However, Burgen and MacIntosh[1] give the acetylcholine content as richest in the basal ganglia, with decreasing amounts in the cerebral hemispheres, brain stem and spinal cord in that order. These investigators[1] add that the cerebellum contains very little acetylcholine, and the cerebral cortex contains more than the underlying white matter, but state that there is no close correlation between the distribution of acetylcholine in the different areas of the brain and the abundance of cell bodies. Estimations of the free acetylcholine in rat brains are shown in the accompanying graph.

Acetylcholine is synthesized in the brain and is present for the most part in a bound form.[4] It is easily released and destroyed. Since changes in the amounts released and stored vary with changes in functional activity, it would seem that acetylcholine has a functional role in the brain.[4] The

DISTRIBUTION OF FREE ACETYLCHOLINE IN RAT BRAINS*



*Adapted from Quastel, J. H.[3]

possibility of its action as a synaptic transmitter is supported by its established role at peripheral cholinergic junctions and by the pharmacologic effects of acetylcholine and of known anticholinesterase drugs. When applied locally to the surface of the cortex, when injected into the grey matter of various structures or into the ventricles, or when injected intra-arterially into the brain or cord, acetylcholine generally has an excitatory action. Less commonly in the same situation, a depressant action is noted. Previous injection of eserine intensifies the effects of acetylcholine, and, by itself, eserine causes both excitatory and depressing actions which are most probably due to the accumulation of endogenous acetylcholine. Most of the central actions of both these drugs are eradicated by atropine in adequate doses.[4]

Drugs have varying effects upon acetylcholine *in vivo*. They may (1) inhibit its formation and release; (2) combine with the receptor substance in the cell either to form an inactive complex that competes with acetylcholine and blocks its action or to form an active complex which induces depolarization; (3) inactivate cholinesterase, thus permitting acetylcholine accumulation; (4) act on the postjunctional element rather than directly on the transmitter mechanism in a manner that alters the stability of its membrane and thus its threshold to the junctional (end-plate or synaptic) potential. This latter action of chemical agents on the postjunctional element is believed to be a major mechanism in anesthesia.[4]

In psychiatry, the interest in acetylcholine stems in part from the knowledge of the favorable effects of cholinergic predominance produced by certain psychotropic drugs. Most of these drugs exert an adrenergic blocking action, the effect of which may be to permit predominance of the cholinergic factor, possibly acetylcholine. The cholinergic-adrenergic balance which affects behavior is thought to exert its effect largely at the synaptic junctions.

Despite considerable investigational activity, as yet there is no conclusive proof that acetylcholine is the agent—or one of a group of agents—involved in central synaptic transmission.[5] There is considerable evidence, however, that the acetylcholine system is involved in both the normal and abnormal functioning of the nervous system.[6]

Marrazzi and Hart[7] have worked on the hypothesis that certain disturbances in neural function can be manifested as mental disturbances and that abnormal modifications of neural function could be an underlying factor in mental disease. On the premise that abnormal patterns of activity of the neural pathways must be based on abnormal changes in the properties of the neuron, these investigators believe that studies are indicated of the functioning of the synapse, which is known to be vulnerable to chemical influences. Epinephrine, LSD-25, mescaline and serotonin especially have synaptic inhibitory action; all have been implicated, at various times, as factors in mental disease. Acetylcholine, on the other hand, has an enhancing or stimulatory effect upon synaptic transmission. It appears that, since epinephrine and acetylcholine can regulate synaptic transmission, disturbances in the amounts present or in the thresholds of the involved tissues would result in an abnormal equilibrium for synaptic transmission.[7]

Acetylcholine functions in several cerebral areas, including the mesodiencephalic activating system. This system is sensitive to members of the reserpine drug group, to various phenothiazines and to azacyclonol.[8] Pfeiffer and Jenney,[9] in studies related to these facts, investigated the antischizophrenic effects of muscarinic stimulation of the brain. They found that certain tranquilizing drugs had an acetylcholine-like effect, resulting in a muscarinic stimulation. The relation of phenylpyruvic oligophrenia to these findings may be significant. The formula of phenylpyruvic acid reveals that it can act as a blocking molecule for the oxygen or ester end of acetylcholine, signifying its possible antimuscarinic effect.[9] This assumes importance when one considers that the inability to utilize phenylalanine results in seizures, mental retardation and insanity. It is therefore suggested[9] that there should be further investigations of naturally occurring metabolites that have a strong muscarinic action, since such substances may be even more antischizophrenic than tranquilizing drugs. In view of these facts, Himwich[8] believes that it is possible for a lack of acetylcholine to be responsible for one type of abnormal behavior and its excess, for another type.

Both quantitative and qualitative changes in the neurohormonal balance need to be studied to understand psychochemical action in the brain. Quantitative changes bring about shifts in the neurohormonal balance, involving excesses or shortages of acetylcholine, epinephrine, norepinephrine, serotonin or serotonin-like substances. In schizophrenia, however, a qualitative change may be involved, particularly a metabolic factor implicated by the investigation of changes associated with

a more rapid oxidation of epinephrine or with the production of abnormal oxidation products of this substance. Alteration of epinephrine metabolism may cause the release of an abnormal metabolic product which may be a pathogenic factor in schizophrenia.[8] Hoffer[10] proposes that both qualitative and quantitative changes occur in schizophrenia. He states that acetylcholine and epinephrine are overproduced, with formation of adrenochrome and adrenolutin, oxidized derivatives of epinephrine. Both of these derivatives are known to give rise to schizophrenic-like changes in the normal person.[10]

Convulsions and Acetylcholine

Although acetylcholine normally is not detectable in the cerebrospinal fluid, it has been found in patients after cerebral trauma and electric shock and in a majority of epileptics, especially those having frequent seizures.[6] It is possible that the free acetylcholine in the brain tissue is increased in epilepsy toward the threshold concentration for its action so that excess release may bring about abnormal activity. But it is also possible that the acetylcholine in spinal fluid may be the result of continuous neuronal hyperactivity on an unknown basis.[6] Studies of epileptogenic focal tissue have shown that it possesses a decreased capacity for binding acetylcholine. This may be related to abnormal behavior due to changes in the chemical potentials of the neurons. Not enough studies have yet been done on the direct effect of narcotics and convulsants upon the rate of liberation of acetylcholine or their indirect effect upon other mechanisms.[6]

Convulsive seizures can be produced in man with intravenous acetylcholine. It is known that both acetylcholine and anticholinesterases may exacerbate cerebral dysrhythmias in some epileptic patients, yet atropine can block these effects or the original dysrhythmia itself. Likewise, atropine can block the electrical and motor signs of excitation in man brought about by the anticholinesterase, diisopropylfluorophosphate (DFP). It is possible that these effects involving acetylcholine may be related to its role as a central transmitting agent.[11]

Convulsive doses of acetylcholine administered intravenously have been used on a trial basis for shock therapy, but procedures such as insulin and electroshock are thought to be safer and more effective.[12] In general, the transient and variable effects of acetylcholine do not fit it for clinical use; other choline esters have been found more suitable.[12] It is of interest that Marrazzi[13] presumes that one way in which electroshock therapy acts in schizophrenia is through the cholinergic effects of acetylcholine released by the convulsions.

Other Links to Psychosis

It is generally presumed that anticholinesterase substances eventually exert their effects in the body via the action of acetylcholine. Along these lines there are several reports linking acetylcholine with various types of psychoses. In one paper[14] DFP was reported to cause severe psychotic episodes. Other reports[15,16] concern benefit from DFP in the manic phase of manic-depressive psychoses. Improvement has also been reported[9] in catatonic schizophrenia from the use of the cholinesterase inhibitors, eserine and arecoline.

All evidence to date concerning acetylcholine and psychoses must be considered to be indirect. This is emphasized once again by the recent report[17] of failure to find increased quantities of acetylcholine in the spinal and ventricular fluids of patients with schizophrenia.

HISTAMINE

Background

Histamine was first synthesized in 1907, and by 1912 it began to be implicated as a causative agent in various pathological conditions. Further studies led to numerous theories linking it with disease syndromes. Yet it took more than 25 years from the time the pharmacologic properties of histamine were described for an effective histamine-blocking agent to be discovered.

Distribution and Release of Histamine

Histamine, a decarboxylation product of the amino acid histidine, is present in practically all tissues bound to a cell constituent which may be protein. It is present in such quantities that the total amount of bound histamine in the body is sufficient to be fatal were it released all at one time.[18] Histamine is found in nerve tissue, the postganglionic sympathetic nerve trunks being richest in content and the central nervous system being lowest.[19]

Bound histamine can be released by chemical or physical noxious stimuli. Many organic bases, such as *d*-tubocurarine and diamidines, release bound histamine. Antigens will bring about its release from the tissues of sensitized animals. Various theories have been proposed to explain the mechanism of release. It is thought that the organic bases may act by competitive displacement from a cellular receptor and that the antigen reaction may be brought about by an intracellular reaction between antigen and antibody, activating a proteolytic enzyme which then liberates histamine bound to intracellular protein.[13]

Clinical Implications in Mental Disorders

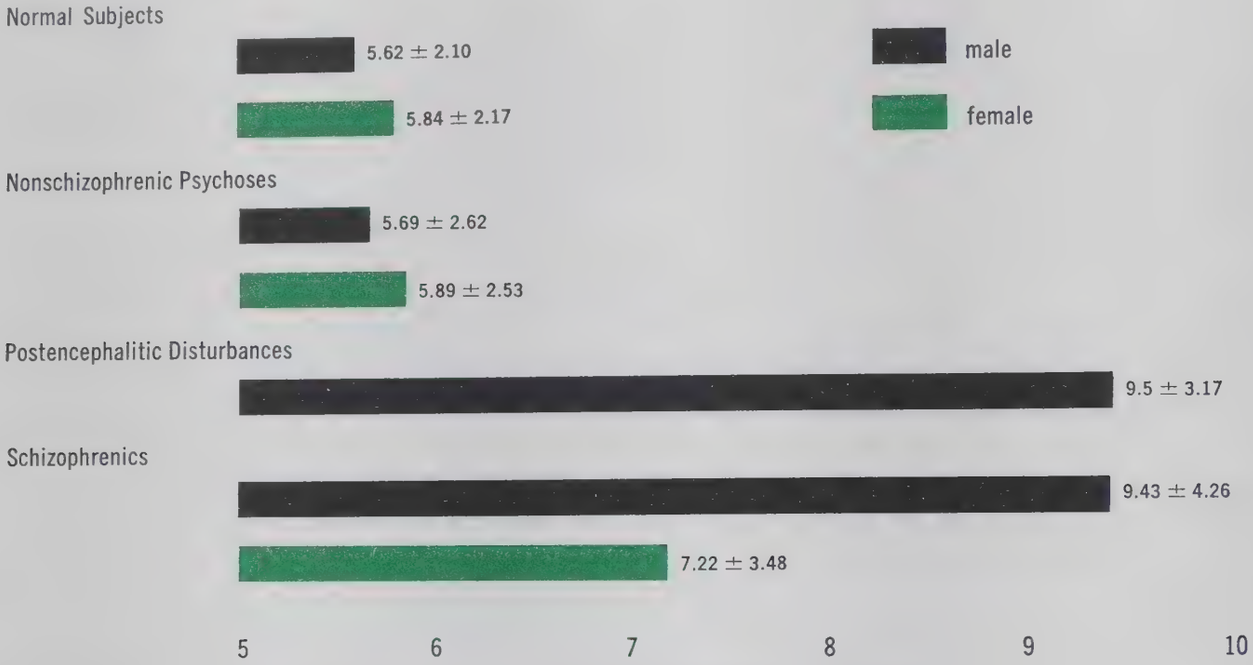
That histamine might be involved in the development of schizophrenia was proposed about 1930. This theory was based on changes observed in the brains of schizophrenics, these changes being similar to those found in rabbit brains after histamine intoxication. In 1939 it was suggested that schizophrenia was due to amine intoxication from histamine and other amines in the blood.[20]

It was because psychotic patients seldom exhibited allergic responses that the metabolism of histamine in such patients first aroused interest.[21] Histamine itself has been tried as a therapeutic measure in schizophrenia since 1935, but results have been inconclusive. Some investigators, however, have noted that schizophrenics have a high tolerance for histamine.[22] In a study of histamine metabolism in schizophrenic patients, an increase of blood histamine was found in male schizophrenics and in nonschizophrenic psychotics with postencephalitic disturbances. Because female

schizophrenic patients in this study did not show this increased blood level, it was assumed that they had a different form of the disorder. Those patients having an increased blood histamine level showed a tendency toward daily fluctuations in this level. This was not statistically significant but may be helpful in attempts to understand various problems concerning histamine metabolism.[16]

BLOOD HISTAMINE LEVELS IN PSYCHOTIC AND NONPSYCHOTIC PERSONS*

(Averages and Standard Deviations)



*Adapted from Gooszen, J. A. H., and Donker, J.[20]

It has been suggested that the higher blood histamine level might be related to allergic disease: that is, that schizophrenia itself is an allergic reaction.[20] Since it has been found that schizophrenics rarely have allergic reactions, these patients may be less sensitive to histamine. According to this theory, this decreased sensitivity may be due to a disturbance of the mechanism whereby histamine is bound to the tissues, resulting in an increased blood level of histamine.[20]

The authors[20] also cite a previous study wherein a cholinergic substance was found in the blood of persons in states of resentment. The study did not identify the substance other than that it was not acetylcholine. On this basis, Gooszen and Donker[20] suggest that the substance might have been either histamine or a histamine-like substance.

Histamine Skin Tests in Psychiatry

Jodrey and Smith[21] carried out releasable skin histamine and histamine tolerance tests on 291 psychotic patients who were schizophrenics, manic-depressives, psychoneurotics, or had personality disorders. Having noted that patients taking reserpine had a 30 per cent lower skin histamine content, they proposed[21] that this was due to serotonin released by reserpine from brain tissue and

platelets; release of this serotonin was thought to liberate histamine. A further finding was that those patients being treated with tranquilizing drugs had an increased tolerance to histamine. Although some phenothiazines are known to be antihistaminic in combating allergic responses, probably due to interference with histamine action at the end organs involved, this property was not believed to affect the measurement of releasable histamine under the conditions in the study. It was the belief of the investigators[21] that the antihistamines would affect the response to endogenous and exogenous histamine in a similar way.

Within the same study,[21] no significant difference was noted between the skin histamine levels of schizophrenics and manic-depressives; neither did the response to injected histamine show a variance. This investigation seemed to show that mental disease itself did not affect tissue histamine levels, but drug treatment did. Accordingly, the paucity of allergic responses in psychotics would not be due to decreased tissue histamine nor to increased tolerance to exogenous histamine. Possibly the sera of psychotics contain some substance that obstructs the anaphylactic release of histamine, yet does not affect its release by a specific drug, such as the curare which was used in this investigation. This hypothetical serum substance might then be related to the etiology of psychoses.[21]

Weckowicz and Hall[22] found that the skin histamine test for schizophrenia had possibilities as a delineator of nosologic boundaries in the disease. Their schizophrenic patients had a delayed and weaker skin reaction to intradermal application of histamine than did nonschizophrenics. This reaction seemed to be specific. Since other work has seemed to demonstrate that morphologic differences exist in the capillaries of schizophrenics as compared to nonschizophrenics, and since capillary dilatation is part of wheal formation, this may be related to the results of the study. Another possible factor in the decreased skin reaction is the existence of an antihistaminic substance in the blood of schizophrenics. It is also necessary to consider the antihistaminic properties of epinephrine and its derivatives. Since the skin histamine reaction is affected primarily in the early phase, an inhibiting substance, such as a chemical, might compete with histamine in chemical reactions until its local supply is used up and the excess histamine then shows a delayed reaction.[22] Another study[23] has attempted to indicate that histamine and thyroid activity may be implicated in schizophrenia.

From the preceding investigations, it seems likely that histamine may indeed be intimately concerned with mental disorders, but, at present, only theories are available regarding mechanisms of action. Little can be said regarding the possible role of histamine as a mediator liberated by vasodilator nerve fibers. That there may be some connection between other chemical mediator systems and histamine is adduced from the finding that some of the sympatholytic betahaloalkylamines have antihistaminic actions and that curare preparations cause histaminic reactions that can be blocked by antihistamines.[24]

Looking Forward

Investigating the nature of brain function is like playing a gigantic game of pick-up sticks. Slowly, the sticks are being collected, but the pattern is complex and many interrelated factors must be understood before any one stick can be withdrawn safely. Each year, as progress is made, we look forward to the future, for the solution is surely there.

Bibliography: (1) Burgen, A. S. V., and MacIntosh, F. C., in Elliott, K. A. C.; Page, I. H., and Quastel, J. H.: Neurochemistry, Springfield, Ill., Charles C Thomas, 1955, pp. 311-389. (2) Hebb, C. O.: Physiol. Rev. *37*:196, 1957. (3) Quastel, J. H., in Elliott, K. A. C., *et al.: op. cit.* (ref. 1), pp. 153-154. (4) Stone, W. E.: Am. J. Phys. Med. *36*:222, 1957. (5) Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, ed. 2, New York, The Macmillan Company, 1956, pp. 389-421. (6) Elliott, K. A. C., in Elliott, K. A. C., *et al.*: op. cit. (ref. 1), pp. 677-695. (7) Marrazzi, A. S., and Hart, E. R., in Himwich, H. E.: Tranquilizing Drugs, Washington, D. C., American Association for the Advancement of Science, No. 46, 1957, pp. 9-12. (8) Himwich, H. E.: Science *127*:59, 1958. (9) Pfeiffer, C. C., and Jenney, E. H.: Ann. New York Acad. Sc. *66*:753, 1957. (10) Hoffer, A.: J. Clin. & Exper. Psychopath. *18*:27, 1957. (11) Toman, J. E. P., in Elliott, K. A. C., *et al.: op. cit.* (ref. 1), p. 556. (12) Goodman, L. S., and Gilman, A.: *op. cit.* (ref. 5), pp. 422-443. (13) Marrazzi, A., in Biological Psychiatry, New York, Grune & Stratton, 1959, p. 272. (14) Feldberg, W.: Physiol. Rev. *25*:596, 1945. (15) Woolley, D. W., and Shaw, E.: J. Pharmacol. & Exper. Therap. *111*:43, 1954. (16) Grob, D.; Harvey, A. M.; Langworthy, O. R., and Lilienthal, J. L., Jr.: Bull. Johns Hopkins Hosp. *81*:257, 1947. (17) Turner, W. J., and Mauss, E. A.: A.M.A. Arch. Gen. Psychiat. *1*:646, 1959. (18) Beckman, H.: Drugs: Their Nature, Action and Use, Philadelphia, W. B. Saunders Company, 1958, p. 448. (19) Sollman, T.: A Manual of Pharmacology, ed. 8, Philadelphia, W. B. Saunders Company, 1957, p. 538. (20) Gooszen, J. A. H., and Donker, J.: Acta allergol. *10*:149, 1956. (21) Jodrey, L. H., and Smith, J. A.: Am. J. Psychiat. *115*:801, 1959. (22) Weckowicz, T. E., and Hall, R.: J. Nerv. & Ment. Dis. *125*:452, 1957. (23) Sackler, M. D.; Sackler, R. R.; Sackler, A. M., and van Ophuijsen, J. H. W.: J. Nerv. & Ment. Dis., *113*:40, 1951. (24) Toman, J. E. P., in Elliott, K. A. C., *et al.: op. cit.* (ref. 1), p. 565.

THE VISCERAL BRAIN

the proposition

"Is emotion a magic product, or is it a physiologic process which depends on an anatomic mechanism?"[1] Developing this fundamental consideration, Papez, in 1937, arrived at a revolutionary concept for a mechanism of emotion. On the basis of available information, he proposed that the rhinencephalic structures, the so-called "nose" or olfactory brain, subserve some of the attributes of the emotional state. In the comparatively brief span of time that has since elapsed, confirmatory recognition has been given to this area of the brain (known also as the limbic system or "visceral brain"[2]) as the neuroanatomic background for emotional expression and effective behavior in its broadest sense.[3] Papez considers that the response to emotion-provoking stimuli (as sex or hunger) is regulated by the visceral brain which acts "...to coordinate sensory events with visceral and bodily reactions and visceral needs."[4]

Phylogenetic development, anatomic studies and clinical and experimental data support this concept of the visceral brain. This current study reviews the present state of our knowledge of the visceral brain with a view toward indicating its implications in the pathogenesis and therapy of many of the illnesses of man.

the emotional state

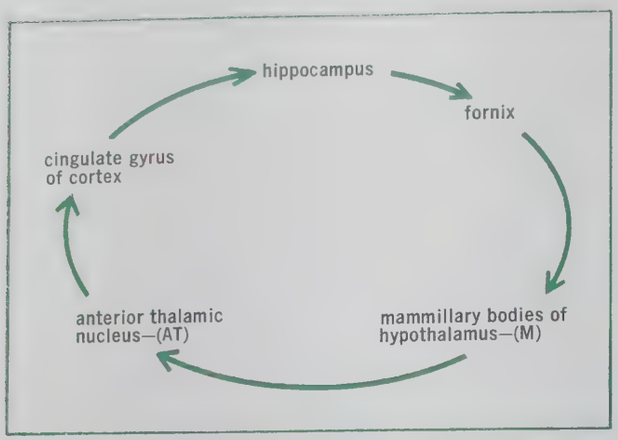
In one medical dictionary[5] emotion is defined as "a state of mental excitement characterized by alteration of feeling tone." The role of the "visceral brain" in the elaboration of the emotions may be clarified by investigations of all the manifestations of emotions, both internal and external; to all these manifestations of emotion the term "multidimensional referent" has been applied.[6]

Emotion is multidimensional in that it is privately felt or experienced (the affect) and outwardly manifested by behavioral patterns which express the private feeling of the subject. In addition, the body has its own internal expression of the emotional state; this is effected by the visceral brain and autonomic nervous system.[6]

THE PAPEZ THEORY

Papez[1] had suggested that "emotional expression and emotional experience may in the human subject be dissociated phenomena." At the more reflex-like level, he postulated, the components of the limbic system act to express emotions (which may take such forms as grimaces, trembling or quickened heartbeat). He added emphasis to his proposal by demonstrating a pathway by which emotional impulses could be received and transmitted (Fig. 1).

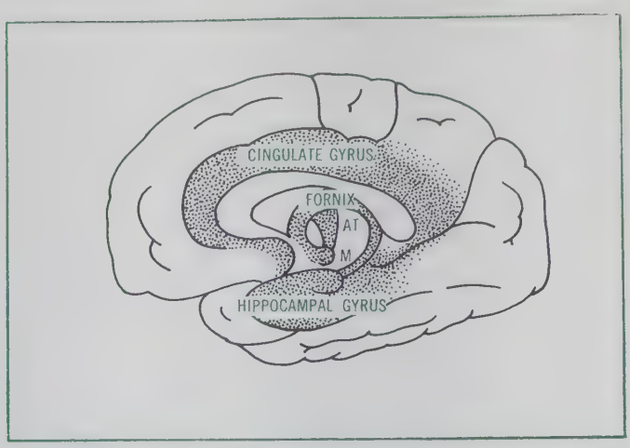
FIG. 1. SIMPLIFIED SCHEME SHOWING A PATHWAY OF EMOTION*



See Fig. 2 for anatomic representation.

*Adapted from Papez, J. W.[1]

FIG. 2. THE VISCERAL BRAIN*



Also known as the limbic lobe and less aptly as the rhinencephalon, this neuroanatomic area is assigned a major role in the mediation of emotion.

*Adapted from MacLean, P. D.[7]

Papez speculated that those processes originating within the visceral brain would add "emotional coloring" to psychic processes in other cortical areas.

THE ROLE OF THE VISCERAL BRAIN

The cerebral convolution known as the limbic lobe (so named by Broca[8] because of its marginal relationship to the brain stem), together with its subcortical cell stations, has been designated as the limbic system. This system, also called the visceral brain, is situated strategically for receiving and associating oral, visceral, sexual and basic sensory sensations (as ocular, auditory) and discharging them through multiple hypothalamic connections.[7]

Deriving from its position and interconnections, some functional comparisons can be made between this primitive cortical area and the most highly developed part of the brain, the neocortex. What a patient *feels* may be said to be mediated by the visceral brain; what he *knows* is a function of the neocortex.[9] However, the limbic and neocortical systems do not work independently of one another; the former "...seems to set the emotional background on which man functions intellectually."[10]

anatomic considerations

Since the term rhinencephalon implies a specific function, there is understandable confusion as to what structures should be included in this ill-suited anatomic designation.[2,11] Some[12] consider the visceral brain as including the rhinencephalon and adjacent area. Anatomy students are more familiar with the structurally restricted rhinencephalon as represented in standard anatomy texts. Papez[13] has employed the more appropriate and more embracing term, "visceral brain," first suggested by MacLean,[7] as synonymous with the rhinencephalon (Fig. 2). He includes olfactory, visceral, habenular, amygdalar, hippocampal, pituitary and hypothalamic structures in the visceral brain.

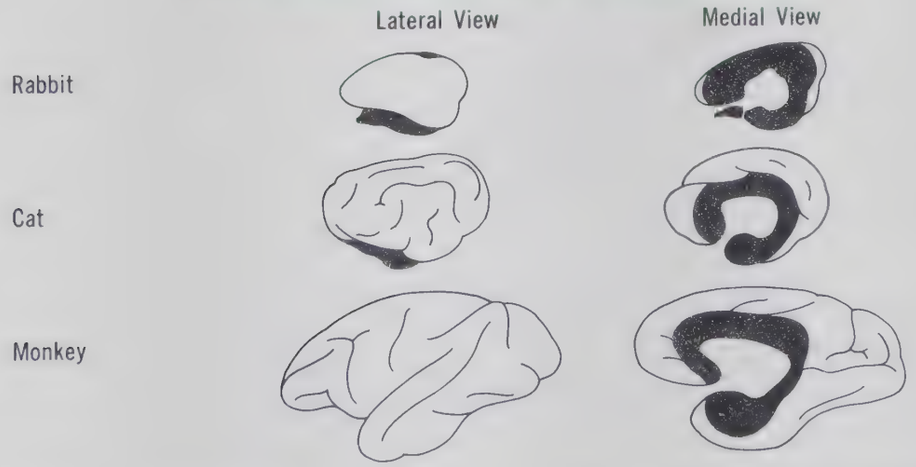
INTERCONNECTIONS

All surrounding brain areas—visual, parietal, auditory, temporal, olfactory, uncinate—relay transcortical impressions to the hippocampal gyrus. In significant contrast to neocortical areas, the limbic structures connect by strong reciprocating pathways with the hypothalamus (the head ganglion of the autonomic nervous system) and other older structures of the brain stem, thereby presenting an effective screen for "...projection of the visceral as well as the exteroceptive senses...."[14] Taken together these interconnecting structures constitute the "harmonious mechanism"[1] which subserves the emotional state.

phylogeny—visceral brain to neocortex

Anatomically and histologically, the limbic cortex is primitive in comparison to the neocortex and, noteworthy too, its development and organization are similar throughout the mammalian series.[14] With the exception of the hypothalamus, other components of the visceral brain are derived from the embryonic olfactory structure.[4] In contradistinction to the enveloping neocortex which has expanded phylogenetically with increase in intellectual functioning, the "old" (limbic) cortex maintains a relative constancy of size in all mammals (Fig. 3).

FIG. 3. COMPARISON OF LIMBIC LOBES IN MAMMALIAN BRAINS*



Drawn roughly to scale, indicating the position of the limbic lobe (black) as a common denominator of the cerebrum.

*Adapted from Anand, B. K.[9]

Its status as a common denominator suggests that this limbic lobe plays an essential role in basic psychologic processes common to both man and other mammals.[9] Here then is phylogenetic evidence that within this "old" cortex the scientist may study what Freud has called biological psychiatry, "...the psychological concomitants of biological processes."[15] MacLean has then postulated two anatomic areas within the limbic system; one subserving the mechanisms of *self-preservation,* the other, concerned with emotional states instrumental in *species preservation.*[16]

the functions of the visceral brain

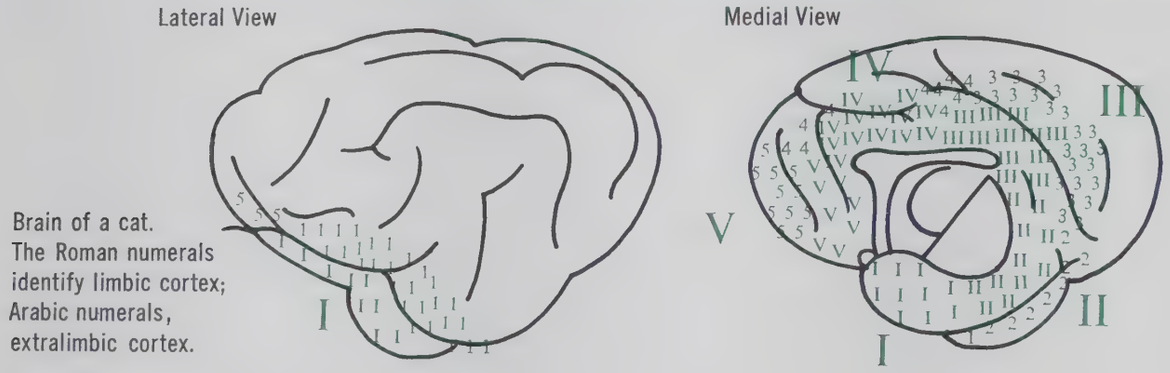
GENERAL STATEMENT OF FUNCTION

Emotional, autonomic, alerting, visceral and olfactory mechanisms are those which have been identified with the visceral brain. According to Papez, the structural components subserving these functional mechanisms are "... biologically grounded and are closely bound in action to regulate innate, automatized activities concerned with searching, feeding, sex, fight, flight, and the emotion-provoking situations in the body and the environment."[13]

FUNCTIONAL LOCALIZATION

In the description of the visceral brain it must be recognized that, although anatomic delineation is precise, the "... wide spectrum of activities influenced by different limbic structures"[9] restricts the imputation of a specific function to a specific part of the limbic system. On the basis of investigation, however, five general functional regions (interrelated limbic and extralimbic areas) have been delineated (Fig. 4).

FIG. 4. FUNCTIONAL AREAS OF THE LIMBIC SYSTEM*



Brain of a cat. The Roman numerals identify limbic cortex; Arabic numerals, extralimbic cortex.

*Adapted from MacLean, P. D.[2]

I. *Frontotemporal* This highly investigated area is the best known.[9] It is primarily concerned with the organization of *oral* activities—attack, defense, feeding, search for food. This site may influence ACTH secretion during stress.[2]

II. *Medial Parieto-occipital Region* Experimental stimulation in this locus provokes *sexual* activities and this region is also thought to influence sex-hormonal secretion, during periods of stress.[2] This will be discussed further under species preservation.

III. *Medial Occipitotemporal* Comparatively little is known of its function. This region constitutes a large part of the hippocampus and is strongly associated by contiguity (and presumably by function) with the aforementioned regions. It may have a "... role in affectively derived experience and memory...."[2]

IV & V. To a great extent functionally unknown, these regions may bear on the role of the frontal lobe in affective behavior.[2]

Predominantly emotionally determined, the activities associated with the visceral brain may be considered in the two broad categories previously mentioned.

PRESERVATION OF SPECIES

The sense of smell (the sole function once attributed to the rhinencephalon) plays a more important role in human behavior than is commonly recognized. In lower animals this is manifested very openly in the relation of odors and their perception to sexual activity. Papez took cognizance of this when he suggested a rhinencephalic representation of the sex organs in his theory.[1]

Smells are important in love and sexual play, thereby assuming an important role in procreation impulses and species preservation. A recent paper[17] has suggested that a diminished acuity of smell may be related to sexual conflict. Experimental observations suggest that "... a portion of the limbic system involving related parts of the septum, hippocampus and cingulate gyrus is concerned with expressive and feeling states that are conducive to sociability and other preliminaries of copulation and reproduction."[14]

Upon stimulation of the aforementioned limbic structures in monkeys and cats, pleasure and grooming reactions and sexual manifestations, even penile erection, have been reported.[14,16] Klüver and Bucy[18] have reported hypersexuality following ablation of this area in animals. Bizarre sexuality has been observed in cats following bilateral ablations of the frontotemporal region—the male cat would mount, indiscriminately, another male cat, a female monkey, female dog, or even a chicken.[16,19] Clinically this has been partially confirmed; Erickson reports the case of a 55-year-old woman with nymphomania in whom a tumor was discovered impinging on the posterior cingulate gyrus.[20]

PRESERVATION OF SELF

Surgical excisions in frontotemporal areas (the amygdalar circuit) have caused wild animals to become tame. In monkeys these excisions have created an apparent inadequacy for self-protection.[14,16] Thus, a monkey so treated, may repeatedly mouth a burning match; it may abandon its normal frugivorous diet and eat raw meat or fish with equal relish. There are also indications that the frontotemporal region may play an important role in man's psychologic appreciation of pain.[14] It is interesting to note that Papez,[1] in his historic paper,called attention to the profound emotional agitation in the rabid patient, which he related to lesions in the hypothalamus and hippocampus, both components of the visceral brain.

The interconnections of the limbic system permit it to function as a unit integrating afferent impulses from the viscera and, through its connections with the hypothalamus, to influence autonomic and visceral activity. Because of the clinical importance of this function, it is discussed under a separate heading.

autonomic aspects and clinical medicine

Its very name indicates the implication of the visceral brain in clinical medicine. Many investigators have reported on the far-reaching effects of emotion on the body processes and a detailed description would be beyond the scope of the present discussion. For the sake of completeness, however,

it is appropriate to indicate some disorders of body function in which the visceral brain has been labeled a pathogenic suspect.

THE LIMBIC SYSTEM AND PEPTIC ULCER

The relationship of the hypothalamus to gastric secretion and its association with the limbic system led to the investigation of the latter's influence on gastric secretory activity. Upon stimulation of specified loci in the visceral brain of cats (such as the amygdaloid nuclei), a marked increase of the pepsin content, volume and acidity of gastric secretion was observed. In some instances erosions, hyperemic patches and even frank hemorrhage were discernible in the gastric mucosa. These observations have obvious implications in the pathogenicity of peptic ulcer.[21]

FIG. 5. GASTRIC BLEEDING FOLLOWING SELECTIVE LIMBIC STIMULATION*

Region Stimulated	Presence of Occult Blood		Frank Hemorrhage	
	Minimum	Maximum	Minimum	Maximum
Amygdala (anteromedial)	2nd day of stimulation	3rd day of stimulation	3rd day of stimulation	4th day of stimulation
Amygdala (basolateral)	3rd day of stimulation	4th day of stimulation	None	None
Frontal Lobe (orbital surface)	3rd day of stimulation	4th day of stimulation	None	None
Temporal (tip)	3rd day of stimulation	4th day of stimulation	None	None
Cingulate (anterior)	None	None	None	None
Hippocampus	None	None	None	None

Findings in the gastric juice of cats after stimulation of various limbic structures.
*Adapted from Sen, R. N., and Anand, B. K.[21]

ENDOCRINOLOGY

Since evidence has localized preservation of species and of self within the limbic lobe, the hypothesis has been advanced that secretion of ACTH and sex hormones is influenced by this region.[2,14] Experimental observations indicate that this system is "...involved in the maintenance of the normal diurnal rhythm in ACTH secretion."[22]

HYPERTENSION

Clinically the effect of emotions on blood pressure is well-documented in the literature, and the visceral brain may well be a neuroanatomic basis for this clinical effect. Thus, Chapman and associates[23] report an 80 mm. Hg rise in systolic tension on stimulation of the frontotemporal region

in man. A pertinent experimental observation by Chu and Loo[24] is the report of blood pressure elevation following stimulation of the mammillary area of a cat.

psychiatric implications

EPILEPTIFORM PATTERNS

Experimental phenomena permit an interpretation of some of the psychic and somatic manifestations of the epileptic seizure.[25] Patterns similar to those observed in psychomotor epilepsy have been reported following stimulation of the hippocampal area in cats.[26] In humans, bizarre automations such as self-inflicted burns or the eating of distasteful food, may be seen in those patients where the neuron disturbance is in the limbic system.[14] Epileptogenic foci in a cortical area receiving fibers from the visceral brain may cause a patient to experience vivid emotions and alimentary symptoms.[14]

The frequent alternation of opposite states of "feeling" in psychomotor epilepsy suggests that there may be an anatomic foundation for "feeling" states comparable to the reciprocal innervation of muscles; "...a feeling of cold may alternate with a feeling of warmth, a feeling of fear with a feeling of anger, a feeling of familiarity with a feeling of unfamiliarity, and so on."[2]

"SCHIZOPHYSIOLOGY"

The postulated dichotomy between emotional (limbic cortex) and intellectual (neocortex) processes, or "schizophysiology," as it has been described by MacLean,[14] has deep psychiatric implications. Without limbic structures, he states, "...we would be like disembodied spirits," since the preservation and procreation of the animal being lies largely within the visceral brain.[14] When we speak of "...the preservation and procreation of ideas..." however, we are entering the area of the neocortex.[16] It is thus the result of limbic involvement that produces the changes in affective behavior following lobotomy.[9] In experimental animals, a suggestive counterpart of catatonic schizophrenia has been provoked during hippocampal seizures.[2]

Of decided interest to psychiatrists is the recognition that stimulation of one limbic area may elicit a rewarding feeling; stimulation of another, a punitive feeling.[22] Bearing on this, Lilly[27] submits a "...proposition to question: *the initiation and the repetition of all (motor) actions of themselves are either internally rewarding (start effect) and/or cause the termination of internal punishment (stop effect).*"

limitations and expectations

Much still remains to be clarified in this concept of a "visceral brain." For instance, the anatomic area wherein the limbic cortex and neocortex interact is still obscure.[28] However, as Fulton so adequately stated, "Human behavior, indeed, can no longer be considered a thing apart and unrelated to anatomical structures and physiological function; by the same token the science of psychiatry has become one in which we are now forced to correlate structure with function."[3] The psychotherapeutic and chemotherapeutic applications of this precept are far reaching.

Bibliography: (1) Papez, J. W.: A.M.A. Arch. Neurol. & Psychiat. *38*:725, 1937. (2) MacLean, P. D.: Psychosom. Med. *17*:355, 1955. (3) Fulton, J. F.: Frontal Lobotomy and Affective Behavior: A Neurophysiological Approach, New York, Norton, 1951, p. 32. (4) Papez, J. W.: J. Nerv. & Ment. Dis. *126*:40, 1958. (5) Dorland's Illustrated Medical Dictionary, ed. 23, Philadelphia, Saunders, 1957, p. 442. (6) Reid, J. R., in Cobb, S.: Emotions and Clinical Medicine, New York, Norton, 1950, p. 25. (7) MacLean, P. D.: Psychosom. Med. *11*:338, 1949. (8) Broca, P., cited by Anand, B. K.: Indian J. Physiol. & Pharmacol. *1*:149, 1957. (9) Anand, B. K.: *ibid.* (10) Cobb, S.: *op. cit.* (ref. 6) p. 87. (11) Pribram, K. H., and Kruger, L.: Ann. New York Acad. Sc. *58*:109, 1954. (12) Ranson, S. W., and Clark, S. L.: The Anatomy of the Nervous System, Philadelphia, Saunders, 1959, p. 327. (13) Papez, J. W., in Jasper, H. H., *et al.*: Reticular Formation of the Brain, Boston, Little, Brown, 1958, p. 591. (14) MacLean, P. D.: Am. J. Med. *25*:611, 1958. (15) Freud, S.: New Introductory Lectures on Psycho-Analysis, New York, Norton, 1933, p. 132. (16) MacLean, P. D.: J. Nerv. & Ment. Dis. *127*:1, 1958. (17) Rosenbaum, J. B.: The Significance of the Sense of Smell in the Transference, paper presented before the Am. Psychoanalyt. Assoc., New York, Dec. 4-6, 1959. (18) Klüver, H., and Bucy, P. C.: A.M.A. Arch. Neurol. & Psychiat. *42*:979, 1939. (19) Schreiner, L., and King, A., cited by MacLean, P. D.: *op. cit.* (ref. 16). (20) Erickson, T. C., cited by MacLean, P. D.: *op. cit.* (ref. 16). (21) Sen, R. N., and Anand, B. K.: Indian J. M. Res. *45*:515, 1957. (22) Langworthy, O. R.: Am. J. Psychiat. *116*:581, 1960. (23) Chapman, W. P., *et al.*, cited by MacLean, P. D.: *op. cit.* (ref. 14). (24) Chu, H. N., and Loo, Y. T., cited by MacLean, P. D.: *op. cit.* (ref. 7). (25) Andy, O. J., and Akert, K.: J. Neuropath. & Exper. Neurol. *14*:198, 1955. (26) Green, J. D., and Shimamoto, T.: A.M.A. Arch. Neurol. & Psychiat. *70*:687, 1953. (27) Lilly, J. C., in Jasper, H. H., *et al.*: *op. cit.* (ref. 13), p. 720. (28) Nauta, W. J. H., cited in MacLean, P. D.: *op. cit.* (ref. 14).

experimental methods for evaluating psychotropic drugs

In just a few short years the vast clinical, social and economic impact of psychotropic drugs has evoked an explosion of research into basic scientific rationales in an effort to support and explain the empiric clinical results. Although apparently illogical, this order of events is by no means unusual —in fact, it appears to be a traditional necessity that theory follows practice and the new field of psychopharmacology is no exception.

It should be stated at the outset that psychopharmacology is still groping. Its methods and results are still tentative. It is growing, however, opening new roads to research and unblocking some of the old. And until much more is known about the various psychiatric, neurologic, neurophysiologic, biochemical and other processes relevantly involved, this is the most that can be expected.

The flood of literature in this field is overwhelming; space does not permit an integrated, systematic review of all the methods currently in vogue in experimental evaluation of psychotropic drugs. This report, therefore, is confined to a small but representative sample of methods used in the screening and analysis of new psychotropic agents. As a result, certain provocative as well as established tests have been omitted—some because they are not widely used, some because they do not apply solely to psychotropic drugs (toxicity tests, for example), and some because they apply to too many types of psychotropic drugs. Abolition of the righting reflex, for instance, is achieved by hypnotics, muscle relaxants, neuromuscular blockers and narcotic analgesics as well as many other classes of drugs.

7

ROUTINE SCREENING PROCEDURES

In the idiom of psychopharmacology, "routine screening" designates the scanning procedures used to detect useful from nonuseful drugs.

"If it were only a problem of finding a drug with activity, new drug development would be relatively simple. But we are still faced with the task of evaluating the specific action or actions of interest within the context of the *total* changes produced by a drug. The sophistication and art require that we develop enough basic insight about the profile of a drug's activity, and the relevance of our screens, to predict the likelihood of a drug's clinical efficacy and safety. Ideally we should be able to predict, within reasonable limits, the clinical dosage, actions, side effects, potential toxicity, and patient material most likely to benefit from the drug."[1]

At best, screening methods should be rapid, specific and at least semiquantitative. To meet these standards most efficiently, pharmacologists agree that it is best to employ a comprehensive battery of tests characterizing the dose-response profile and pattern-specificity of a new drug. Empiric as well as standardized approaches are permitted.

Standardized observation with manipulation is the first technique employed in most preliminary screening programs.

Irwin's method[1] is multidimensional and is so designed that the desired information can be acquired in two to three hours. "The procedure, which we refer to as a CNS Activity and Acute Toxicity Screen, relies on standardized, multifactorial observation, a wide dosage range, a single species and route of administration, and simultaneous recording and quantification. As a result, the data obtained is in integrated form."[1]

After intraperitoneal injection, unanesthetized docile male mice are observed and manipulated (handled for specific purposes, e.g., to observe reactivity, resistance) to measure onset, peak, duration, character and intensity of drug action. Toxicity is observed for five days. Observations are scored. In addition, "...an attempt is made to characterize the overall behavioral, neurologic, autonomic and toxic effects.... The signs observed in each of these categories are presented... [Figs. 1, 2 and 3]."[1] Examples of how they are operationally defined and quantified are shown in Figs. 4 and 5. Irwin emphasizes that these procedures "...are *applicable only to drug actions which are grossly observable;* other techniques are required to measure the 'hidden' actions of drugs."[1]

Sleeping Time—To determine whether a drug potentiates barbiturate sleeping time, Toman and Everett[2] use ineffective dose levels of the test drug in groups of mice which, 30 minutes later, receive 60 mg./Kg. of pentobarbital intraperitoneally.

FIGURE 1.* CNS ACTIVITY AND ACUTE TOXICITY SCREEN (MICE)

1. Animals:	Male, CF #1 mice (18–22 Gm.); docile.
2. Route:	I. P. (rapid onset, peak; insolubility O.K.).
3. Dosage:	Logarithmically spaced (10, 30, 100, 300, 1000 mg./Kg. of free base, 3 animals per dose).
4. Solvents:	HCl, NaOH, H_2O, 5–10% gum acacia only.
5. Sol'n. Conc.:	0.2% for 10–100 mg./Kg. doses; 2.0% for 300–1000 mg./Kg. doses. Injected volume varies from 0.1 to 1.0 ml.
6. Procedure:	Standardized, gross observation and manipulation.
7. Observations:	Onset, peak, duration, character and intensity of actions; toxicity over 5 days.
8. Scoring:	Peak effects (0–8 scale) of 3 animals/dose averaged. Baseline score for **normal** signs = 4; **abnormal** signs = 0.
9. Data Reporting:	In tabular form, significant changes only (ready visualization); drug specificity, classification, therap. ratio, therap. index and interest indicated.

FIGURE 2.* MOUSE BEHAVIOR PROFILE

Awareness	Motor Activity	Mood-Affect
Alertness	Spontaneous Act.	Grooming
Stupor	Reactivity (Envir.)	Vocalization
Visual Placing	Touch Response	Restlessness
Spatial Orient.	Pain Response	Irritability
Struggle Resp.		Aggressiveness
Catalepsy		Fearfulness
Stereotypy		

FIGURE 3.* MOUSE NEUROLOGIC PROFILE

CNS Excitation	Motor Incoord.	Muscle Tone	Reflexes
Startle Response	Body Position	Limb Tone	Pinna
Straub Tail	Limb Position	Grip Strength	Corneal
Tremors	Staggering Gait	Body Sag	IFR
Dysmetria	Unusual Gait	Body Tone	Scratch
Twitches		Abdominal Tone	Writhing
Opisthotonus			Righting
Convulsions			

FIGURE 4.* MOUSE AUTONOMIC/TOXICITY PROFILE

Eyes	Secretions/Excretions	General	Mortality
Pupil Size	Lacrimations	Piloerection	Delayed
Palpebral Opening	Urination	Hypothermia	Acute
Exophthalmos	Diarrhea	Skin Color	
Opacity	Salivation	Heart Rate	
		Resp. Rate	
		Resp. Arrythymia	

*Adapted from Irwin, S.[1]

Sleeping time till waking is recorded. Results show that the action of most tranquilizers is synergistic with barbiturates in prolonging sleeping time. Although this is an important finding, the test is not considered specific: similar results are obtained with a large variety of other drugs.[2]

Electroshock Latency—"A more restricted test for reserpine-like activity...reserved for drugs of particular interest."[2] Electroshock seizures are produced in mice at each dose level by means of a Grass stimulator delivering 1 millisecond impulses at 140 volts and 100 per second frequency for 0.3 seconds through corneal electrodes. Latency from beginning of shock to onset of the tonic phase of the seizures is timed by stop watch. "Among the established tranquilizers, the active reserpine alkaloids are unique in their ability to reduce latency....Latency reduction is not peculiar to mice, for we have observed it in psychotic patients undergoing electroshock treatment while receiving reserpine; it is the antithesis of the prolongation of electroshock latency seen in patients with high levels of clinical anxiety."[2]

Stress and Electroshock Latency—In this more specific test, animals are shaken for 30 seconds at the rate of 3 shakes per second in a modified bottle shaker. This is followed by immediate administration of electroshock. Some of the drugs tested for effect on latency were reserpine, desmethoxyreserpine, Lucin H and chlorpromazine, "all of which yielded significant protection against increase due to stress, and...[ethchlorvynol], meprobamate, pentobarbital, azacyclonol, P-189, and [N,N-dibenzyl-β-chloroethylamine]...none of which gave any significant protection. The contrast between reserpine and chlorpromazine on the one hand, and azacyclonol and meprobamate on the other, emphasizes a fact already evident from clinical practice: there are at least two distinct classes of tranquilizers."[2]

ILLUSTRATION OF SCORING PROCEDURES USED TO CHARACTERIZE AND QUANTIFY INTENSITY OF DRUG EFFECTS.

(Figures and scoring adapted from Irwin, S.[1])

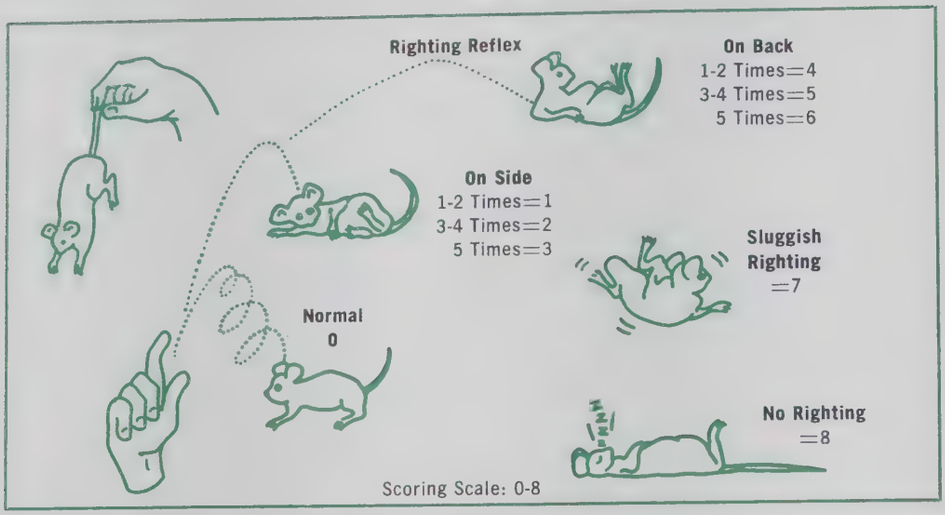
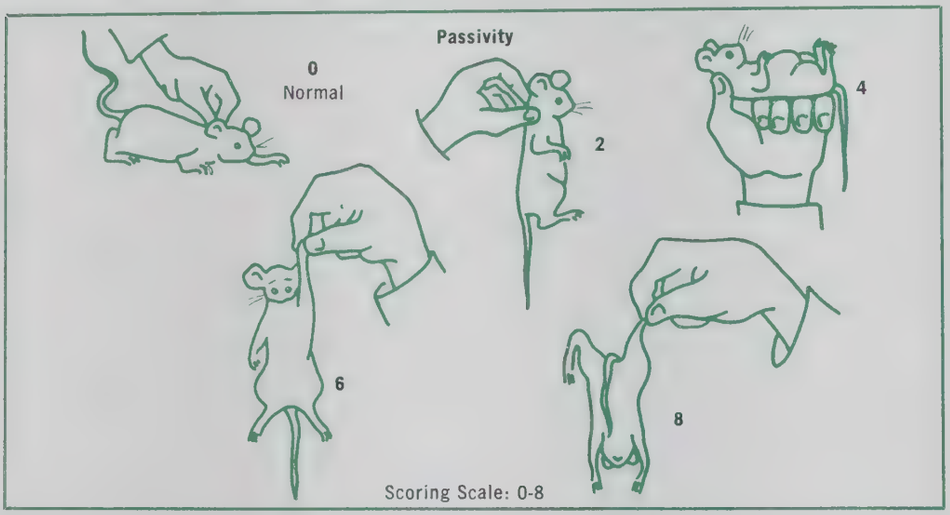


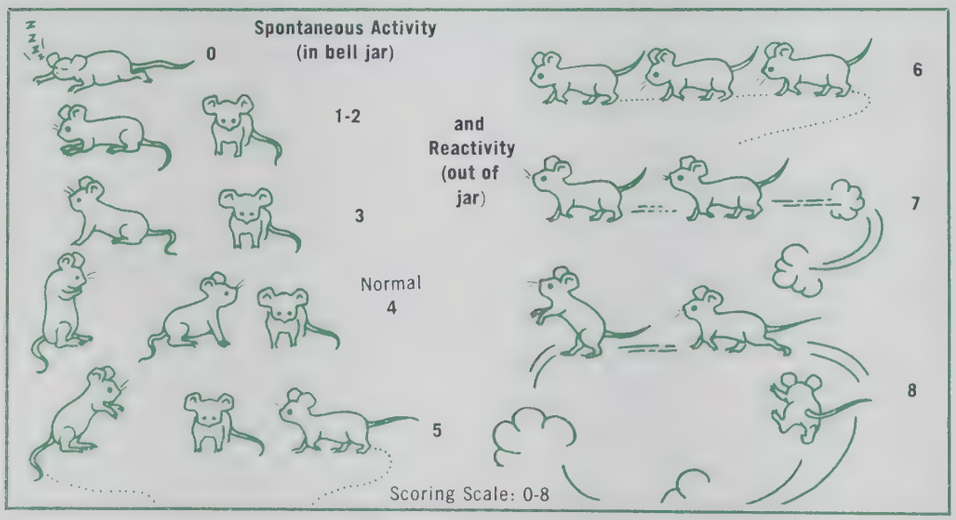
Figure 5a. Impairment of righting reflex

"Animals are flipped by the tail to somersault 2-3 times. The procedure is repeated 5 times." The number of improper landings (on back or side) is observed and forms the basis of scoring.



5b. Passivity

The struggle behavior of animals manipulated gently into unusual positions (held up by skin over neck, rotated onto back, suspended by forelimb, etc. as shown) is scored.



5c. Spontaneous activity/ reactivity

"Three animals at each dose level are housed together in a glass container containing sage. Increased spontaneous activity is quantified on the basis of their locomotor behavior inside the jar; increased or decreased reactivity, on the basis of their behavior when transferred to a new environment (tabletop); decreased spontaneous activity, on the basis of their behavior both inside and more particularly outside their container (subsequent to their initial 'reactivity' response)."[1]

Spontaneous Behavior in Other Species– For substances of special interest, other laboratory animals, especially cats, dogs and monkeys, are additionally used in the investigation.[2] Following a period of control observation, the test drug is administered and the animals observed and handled intermittently during at least a 24-hour period. Special attention is paid to affective changes such as "taming," in comparison with the known previous personality of the animal.

For example, "diminution of play and grooming activity, and of fearfulness or aggressiveness when present, were among the earliest behavioral changes observed with low doses of perphenazine [TRILAFON] or chlorpromazine."[3] In addition, these agents suppressed hostility in aggressive animals.

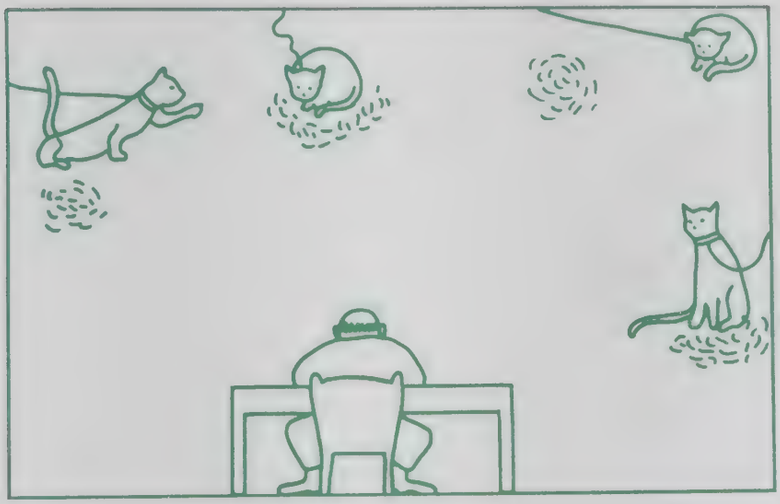


FIGURE 6. CAT PLACEMENT

In his work with cats, Irwin[1] has the animals restrained by leashes spaced to permit a limited degree of social interaction. In this way, information on social behavior is obtained without unduly increasing the variables in the experimental situation (Fig. 6).

"The advantage of the cat procedure is that it appears to be sufficiently sensitive to measure the effects of therapeutic doses of drugs, *i.e.*, doses almost identical on a mg./Kg. basis to those employed clinically in humans."[1]

LOCOMOTOR ACTIVITY

Compounds showing promise of being tranquilizing agents are next tested for their effects on spontaneous motor activity. Various devices including photocell chambers, revolving treadwheels and jiggle-cages are used to measure these effects. Cook,[4] for example, places mice in individual chambers through which series of light beams pass, each beam focused on a photoelectric cell. The mouse moving about breaks the light beams. All such breaks are automatically recorded. "The number of counts in a specific time interval gives us a measure of spontaneous motor activity."[4] In this way, Cook found that chlorpromazine, promazine, 2-chloropromethazine and prochlorperazine all depress motor activity—indicating that these agents exert a "depressant" effect on the central nervous system.

Using revolving treadwheels equipped with automatic revolution counters, Irwin, Slabok and Thomas[5] noted a highly significant correlation between the locomotor activity levels of the animals

(Carworth rats) before treatment and their subsequent locomotor response to drugs. Both "stimulants" (pipradrol or methamphetamine hydrochloride) and "depressants" (chlorpromazine hydrochloride, pentobarbital sodium or morphine sulfate) produced a considerably greater effect in animals with high control activity than in animals with low spontaneous activity. Behaviorally, there was no correlation between control activity counts and their affective state (fearfulness, placidity, aggressiveness). Physiologically, there was no correlation between control counts and body weight, B.M.R., latency for the tonic extensor component of maximal electroshock seizures, the sensitivity to ataxia, impairment of the righting reflex and response to a variety of other drug actions. The correlation, therefore, appears to be on a selective basis and unrelated to the general physiologic status of the animals. It is suggested that the data "...may establish an experimental corollary to the observed failure of depressive (hypoactive) patients to respond to psychomotor stimulants and the greater efficacy of chlorpromazine and reserpine in the more manic (hyperactive) patient."[5]

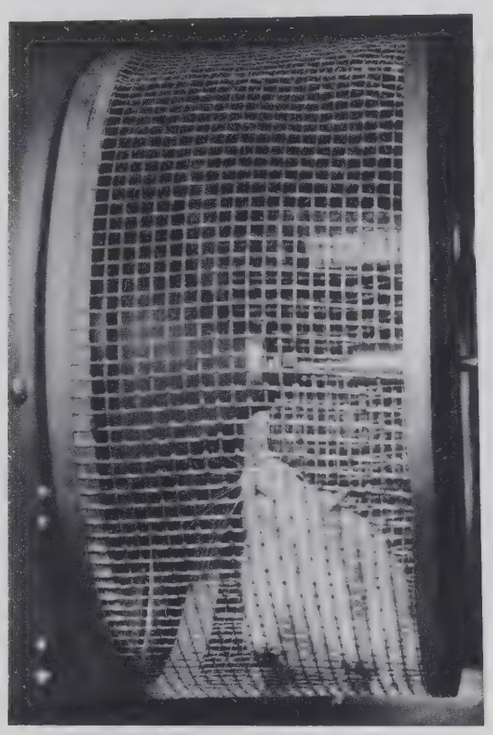


FIGURE 7. MEASURING LOCOMOTOR DEPRESSION

Revolution counters record spontaneous running and walking of control and drug-treated animals in revolving treadwheel.

TECHNIQUES FOR TESTING BEHAVIOR

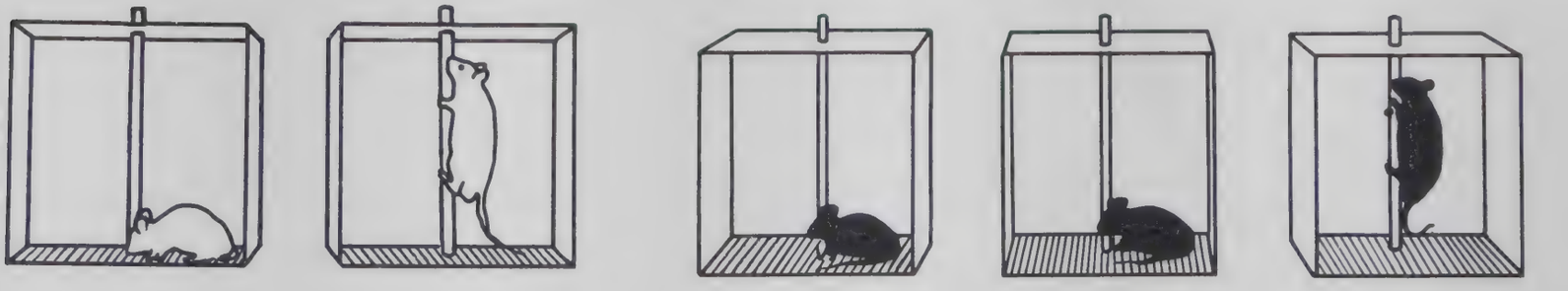
Potentially useful drugs are tested further for their effects on various aspects of behavior, such as hostility, fear, fighting, etc. The method most often employed to evaluate behavior is observation including that of the conditioned avoidance-escape response.

Conditioned avoidance-escape responses developed in rats have been employed widely in the evaluation of the comparative effects of several central nervous system active pharmacologic agents. "Differentiation has been made between those CNS active materials that have a *specific* effect on a conditioned response (chlorpromazine, reserpine, morphine), and those that have a somewhat *nonspecific* effect on a conditioned response (barbital, pentobarbital, methylparafynol, meprobamate)."[6]

Essentially, the experimental technique involves the use of a conditioned stimulus (bell, buzzer,

light, etc.) in conjunction with an unconditioned stimulus (generally noxious and punishing such as an electric shock). During a training period the animals learn to *avoid* being shocked by moving into a defined safety area (such as climbing a pole or jumping over a hurdle) or, in case they do not avoid, to *escape* from the shock into the safety area. During *conditioning* trials, the animals learn to respond to the buzzer (or whatever stimulus is used) alone. When this recurs on a stable basis, a conditioned response has been developed.[6]

FIGURE 8. TYPICAL CONDITIONED AVOIDANCE-ESCAPE RESPONSE



a) after training, untreated rat

b) jumps on pole at sound of stimulus

c) after training, treated rat (phenothiazine tranquilizer)

d) does **not** respond to **stimulus,** does **not** jump on pole

e) but **does** respond to **shock,** indicating that muscular coordination is not impaired

In their comparative study of the effects of chlorpromazine and perphenazine (TRILAFON) on the conditioned avoidance-escape response, Irwin and his co-workers[7] observed that "...perphenazine orally was 7.4 and subcutaneously 13.7 times more active than chlorpromazine in blocking conditioned avoidance behavior in the rat [animal does not jump at stimulus but *does* jump from shock. See Fig. 9]." As shown in Fig. 10, better dissociation between depression of avoidance-escape behavior was obtained with perphenazine than with chlorpromazine.

This suppression of conditioned avoidance-escape behavior together with the depression of locomotor activity appears to constitute the principal behavioral actions of perphenazine and chlorpromazine.

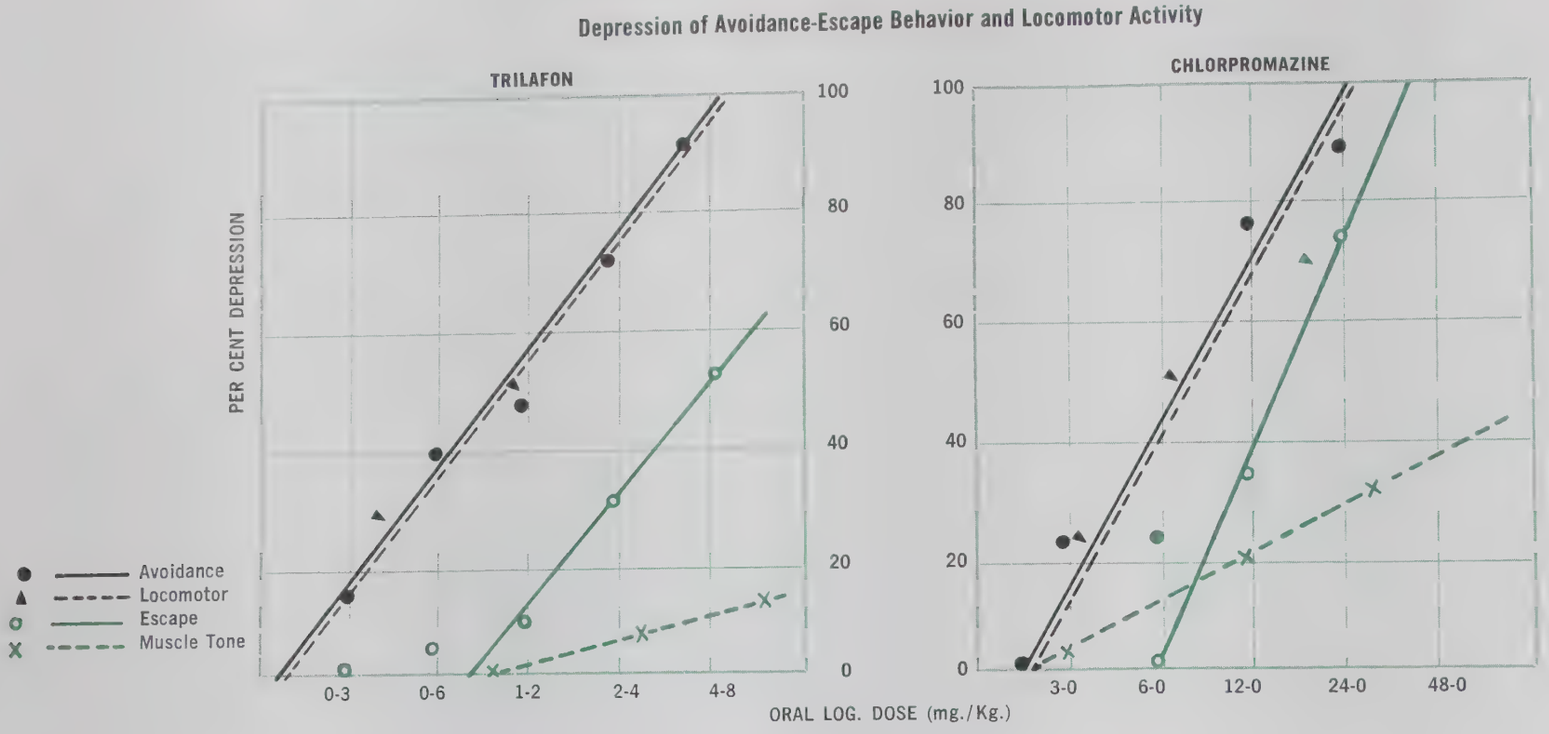
FIGURE 9. EFFECTS ON CONDITIONED AVOIDANCE BEHAVIOR (RAT)

(Adapted from Irwin, S., et al.[7])

Drug	Route	No. of Animals	ED_{50}* (mg./Kg.) Avoidance	Escape	Relative Potency	Slope
Perphenazine	Oral	79	1.0 (0.7–1.4)	3.3 (2.7–4.5)	7.4 (4.3–11.8)	0.754
Chlorpromazine	Oral	69	7.5 (5.3–10.4)	19.0 (14.0–25.0)	1.0	0.754
Perphenazine	Subcutaneous Injection	27	0.1 (0.06–0.17)	1.2 (0.8–1.3)	13.7 (5.7–39.2)	0.784
Chlorpromazine	Subcutaneous Injection	27	1.4 (0.88–2.30)	16.7 (12.8–22.0)	1.0	0.784

*Dose producing suppression of 9 out of 18 responses tested per animal over five hours, with 90 per cent confidence limits.

FIGURE 10. TRILAFON AND CHLORPROMAZINE RESPONSE CURVES (RAT)



For depression of locomotor activity, suppression of conditioned avoidance and escape behavior and relaxation of muscle tone. (Adapted from Irwin, S., **et al.**[7])

METHODS OF ANALYZING DRUG-BEHAVIOR INTERACTION

Although not yet standardized for use in routine screening, methods employing work performance, experimentally induced "anxiety," and free operant techniques contribute importantly to the body of knowledge indispensable to the evaluation and analysis of drug-behavior interaction.

Experimental "Anxiety"—While Pavlov's "experimental neurosis" technique has been used extensively in studying the development of abnormal behavior patterns in animals, little has been reported on the application of this approach to the evaluation of drugs. Masserman and Yum,[8] in their experiments with cats, found that alcohol effectively prevented onset of experimental neurosis and, furthermore, that it could restore normal behavior in "neurotic" cats.

To test the influence of drugs on experimentally induced neurotic behavior, Jacobsen and Skaarup[9,10] used a modified Masserman technique.

The Method—Cats were trained to open a food box to obtain a food pellet available only after a bell signal was given. "Further, the cats were taught to release the bell signal themselves by means of a switch placed in the experimental cage. Once this feeding habit had been well established, the cats were exposed to a blast of air from the food-box whenever they took the food pellet. This procedure was repeated during a series of successive experiments, so that the cats developed a conflict between attraction to the food-box and fear of it. The conflict resulted in a characteristic behaviour generally described as 'neurotic' in the literature. This behaviour can be affected by several drugs."[9]

In evaluating effects of certain agents: "A clear-cut normalizing effect was seen after administration of a series of benzilic acid aminoester derivatives. The best results were obtained with the N-diethylaminoethyl derivative.

"Some effect was also seen after alcohol. Scopolamine and chlorpromazine showed no effect by the technique employed."[10]

"Free Operant" Conditioning—This technique is widely used and has contributed much valuable data. "Among the many advances in psychological science over the past several years, animal laboratory approaches to the experimental analysis of behavior have made one group of contributions that seems to stand out with particular prominence among methodological advances in comparative psychopharmacology... [the development of operant conditioning techniques in the analysis of behavior]."[11]

The original rationale and technique of Skinner's operant conditioning are complex,[12,13] and space does not permit a full discussion of them. However, in a recent report, Brady[14] gave the following succinct analysis of the rationale with modifications as used today:

> "The quest for more precise behavior control methods has led us in recent years to the analysis of a hitherto neglected set of variables which appear to contribute powerfully to the consequences of drug administration for behavior. Broadly described, these variables may be identified as the relations between behavior and its controlling environment, and the development of techniques that permit a high degree of experimental control over the behavior of the individual has made it possible to identify and explore many of the contingencies that generate behavioral processes.
>
> "These techniques have developed independently of pharmacologic applications, but the precision, sensitivity, and reproducibility in behavior control which they provide have made it possible to extend the basic methodology in various directions. The conceptual framework for this animal experimental approach to the investigation of psychopharmacologic relationships rests upon a simple principle: namely, the characteristics of an organism's behavior are to a considerable extent, at least, determined by what the environmental consequences of that behavior have been in the past. The animal laboratory has provided an opportunity for the systematic analysis of orderly relations among behavior segments within this framework, and the term 'operant behavior'[13] has been used to refer to behavior which operates upon the environment in this fashion. The process of manipulating such behavior as a function of its environmental consequences has been termed 'operant conditioning'...."[14]

As to the method itself, Skinner devised an apparatus, now known as the Skinner Box, in which "random" bar-pressing or lever-displacement by the animal is "reinforced" by food or water, either at fixed time intervals or after a particular number of responses has been made. By cumulative recording of these responses on a kymograph, performance curves are obtained. The slopes indicate response rates at any given time, as well as the effects upon these, of deprivation, satiation, reinforcement, and extinction. Stimulus conditioning can then be studied in a quantitative manner.[15]

In a recent study,[14] Brady describes how this method, with modifications, reliably produces and selectively measures emotional behavior patterns in experimental animals. He also illustrates its use in investigating the effects of drugs on experimental behavior.

Rats and monkeys were placed in modified Skinner Boxes,[14] deprived of food and water for at least 24 hours, and trained to press a bar for a reward: water for the rats, sugared orange juice for the monkeys. At first, the animals were given a drop of reward *every* time they pressed the lever (*continuous* reinforcement). They were then shifted to a schedule on which the bar-press produced the reward only aperiodically (*variable-interval* reinforcement). Responses were automatically recorded.[15]

When the lever-pressing rates for all animals were stabilized on a variable-interval schedule, a conditioned emotional response of the "fear" or "anxiety" type was superimposed upon the bar-pressing behavior. This was accomplished through a conditioned punishment procedure: a clicking noise terminating in a painful electric shock to the animals' feet. "With the pain shock following each 5-minute clicker presentation, virtually complete suppression of the lever-pressing behavior is apparent during the clicker periods... although the stable lever-pressing rate is maintained throughout the 5-minute intervals between emotional conditioning trials."[14]

After several sessions of regular-interval shock-clicker presentations, all animals were shifted to a variable-interval schedule which provided only occasional contiguous termination of the clicker with the shock. Again, a marked depression in lever-pressing rate was apparent, but "... by no means so complete as that observed during earlier training stages when shock was administered after each clicker presentation...."[14]

"Since this procedure involved some stable and reproducible degree of control over an aspect of the organism's response repertoire ostensibly related to 'emotional' or 'affective' processes, it was decided to explore the effects of one of the more prominent tranquilizing agents, reserpine, upon the behavior baseline maintained in this way. In addition to suggesting an approach to the evaluation of any so-called 'emotional' effects which the drug might be expected to have, this technique of superimposing the conditioned-suppression pattern upon a stable baseline of ongoing lever-pressing activity appeared to provide a concurrent control for more generalized, nonspecific behavior and motor disturbances, malaise, etc."[14]

In the monkey, treatment with reserpine had the following effect: although the general lever-pressing rate was reduced by more than 50 per cent, the *conditioned suppression* of responding during the 5-minute clicker presentations was virtually eliminated. "The animal under the influence of this drug continued to respond throughout the 5-minute clicker presentations at the same rate as during the 5-minute intervals between conditioning trials, even though the pain shock was paired with 30 to 50 per cent of the clicker terminations."[16] Essentially similar results were obtained in rats.

Withdrawal of the drug during control periods resulted in a "... rapid and abrupt reappearance of the conditioned 'anxiety' behavior, while readministration of the drug quickly brought back the lever-pressing rate during presentation of the 'anxiety stimulus'."[16]

To probe further the *specificity* of the drug's action, an additional group of rats was trained according to a conditioned "punishment" procedure: lever-pressing *punished* by pain shock in the presence of the clicker. (In "anxiety" conditioning, pain shock is independent of the lever response and is given at the termination of the clicker.) Results: reserpine had no effect whatever upon conditioned "punishment" responses. "Despite the apparent similarity between these 2 emotional-response patterns, the effect of reserpine appears to have been highly specific for the conditioned 'anxiety' procedure."[16]

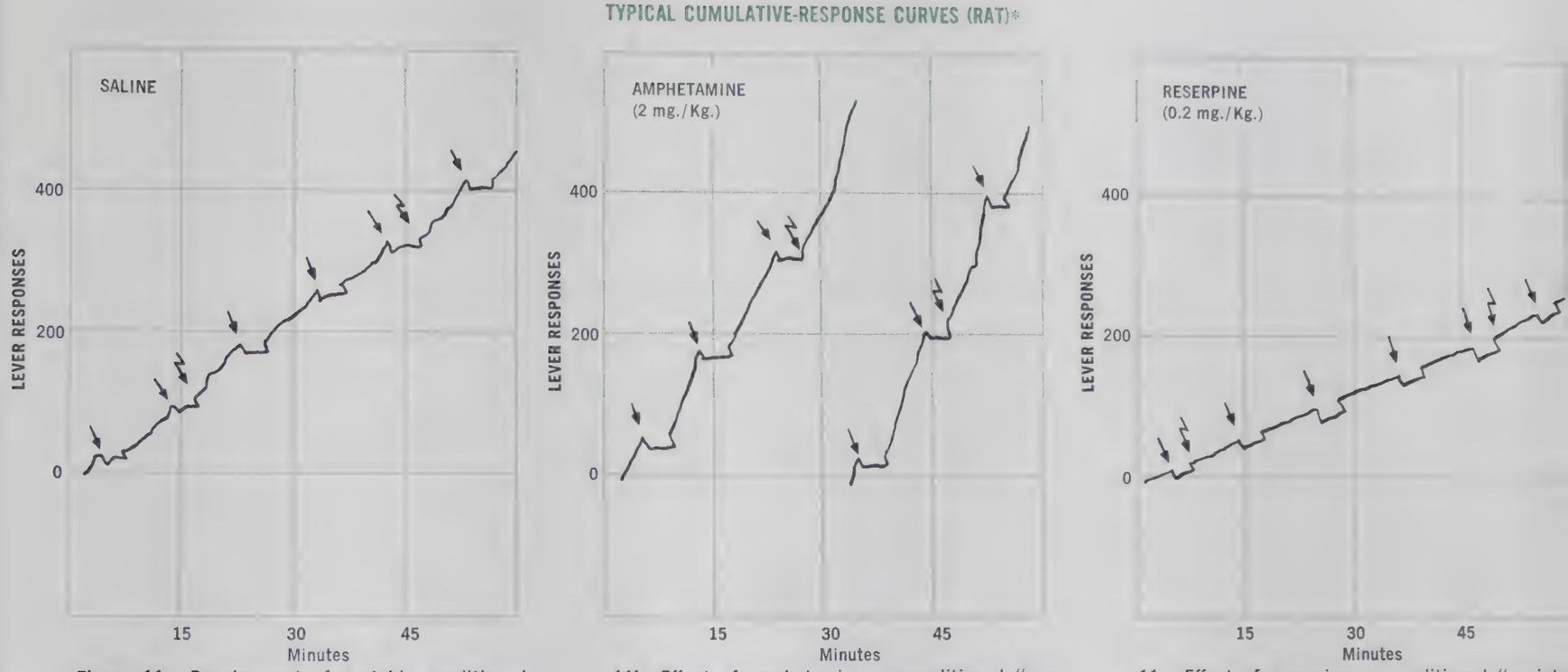


Figure 11a. Development of a stable conditioned-suppression pattern.
*Adapted from Brady, J. V.[16]

11b. Effect of amphetamine on conditioned "anxiety" response.

11c. Effect of reserpine on conditioned "anxiety" response.

For additional indications of drug specificity, "anxiety" conditioning was tested with amphetamine. "Although reserpine, as we have seen, markedly depresses the lever-pressing rate in the absence of the 'anxiety' stimulus, this rate is actually seen to *increase* during the 3-minute stimulus periods. In contrast, amphetamine produces an increase in the number of lever responses in the absence of the 'anxiety' stimulus, although the response rate in the presence of the stimulus shows a significant *decrease*. Indeed, the possibility of expanding the horizons of such drug-behavior relationships to include a broad spectrum of response repertoires for a wide variety of pharmacologic agents would appear to be not unduly remote as the sensitivity and reliability of animal-conditioning techniques show appropriate development."[16] (See Figs. 11a, 11b, and 11c.)

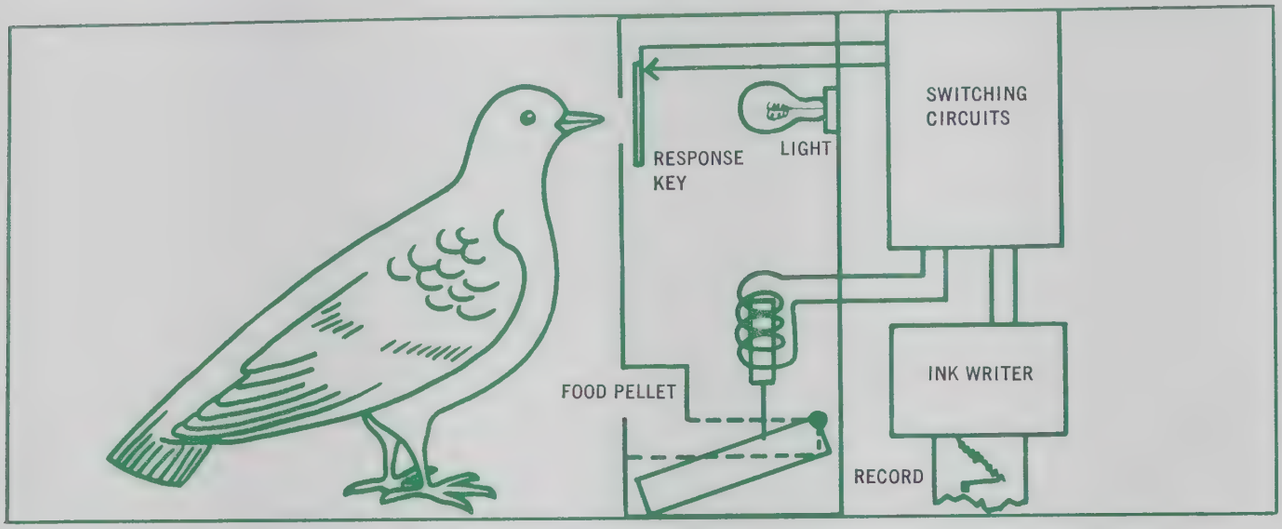
Pigeon Pecking Patterns have been found to yield interesting information on the effects of drugs on work performance. Using a variant of the "free operant" technique, Dews[17] trains pigeons to peck at a translucent plastic disk through which various colored lights can be seen. An automatic counter is connected to switching circuits. Each peck breaks the circuit and is thereby recorded and counted.

"Fixed Ratio" Performance—The distribution of pecks in time is extremely sensitive to the precise contingencies relating pecks to rewards. For example, if every sixtieth peck is rewarded, the pigeon comes to peck at high, sustained rates. This is a fixed ratio schedule: there is a fixed ratio of reinforcements to pecks.[17]

Interval Performance— "On the other hand, if a single peck is rewarded when, and only when, a constant interval of time (for example, 15 minutes) has elapsed, there is a period at the beginning of

the interval when the bird does not peck at all, and then there is a fairly smooth accelerating rate of pecking until the rewarded peck. This is a fixed interval schedule; a fixed interval of time must elapse before a reward can be obtained.... It can be arranged that when a light of one color is on, the schedule is fixed ratio, and when a light of a different color is on, the schedule is fixed interval. The bird comes to perform appropriately to each of the schedules according to which light is on. Thus the bird's performance can be observed on more than 1 schedule during a short period of time without disturbing the animal in any way."[17]

FIGURE 12. DIAGRAM OF APPARATUS USED TO TEST AND RECORD PECKING PATTERNS
(Adapted from Dews, P. B.[17])



Drugs are administered when the bird's performance becomes stable and reproducible. Three hours after injection of 30 mg. of phenobarbital sodium, "...interval performance was almost abolished and ratio performance much disturbed. At 24 hours, ratio performance was almost normal, while interval performance was still profoundly disturbed...."[17]

"Similar experiments were conducted following injection of 3 mg. of methamphetamine. This dose of drug did not appreciably affect ratio performance... while interval performance was greatly changed. ...As might be expected,...methamphetamine leads to an increase in the total number of pecks made...in contrast to the early decrease caused by the depressant phenobarbital."[17] (See Fig. 12.)

SCREENING TESTS AND BEHAVIOR

To explore the spectrum of potential uses of psychopharmacologic agents, the study of behavior in animals is highly advantageous. In addition to the obvious advantages of avoidance of human risk and of availability, the degree of experimental control which may be exercised over the genetic and personal history, as well as their current environment, is extraordinary.

Although many of these tests were devised as screening procedures, refinement has resulted in far greater usefulness for them. As Skinner recently stated,[18] "We are only beginning to appreciate the possibilities here as our experimental techniques reach out to embrace more and more of the relevant variables. The control of motivation is now feasible over a very wide range, and we are slowly learning how to manipulate emotional variables in the laboratory...."

"It would be unfortunate if, with all these special advantages, animal research were relegated to the inferior position of a screening activity. Rather, and...I am speaking as a partisan, I look forward to the emergence in this field of a true science of behavior with appropriate techniques for the measurement of the effects of many sorts of manipulable variables, a careful description of behavioral processes, and a frank acknowledgement of the ultimate goal of the prediction and control of behavior."[18]

Bibliography: (1) Irwin, S.: General Philosophy and Methodology of Screening: A Multi-dimensional Approach, paper presented at Gordon Research Conference on Medicinal Chemistry, Colby Junior College, New London, New Hampshire, Aug. 3-7, 1959. (2) Toman, J. E. P., and Everett, G. M., in Pennes, H. H.: Psychopharmacology, Hoeber-Harper, New York, 1958, pp. 247-266. (3) Irwin, S.: The Value of Animal Experimentation in Establishing Behavior Profiles of Drugs and Factors Influencing Drug-Behavior Interactions, to be published. (4) Cook, L.: Psychiat. Res. Rep. *9*:1 (March) 1958. (5) Irwin, S.; Slabok, M., and Thomas, G.: J. Pharmacol. & Exper. Therap. *123*:206, 1958. (6) Cook, L., and Weidley, E.: Ann. New York Acad. Sc. *66*:740, 1957. (7) Irwin, S.; Slabok, M.; Debiase, P. L., and Govier, W. M.: Arch. internat. pharmacodyn. *118*:358, 1959. (8) Masserman, J. H., and Yum, K. S.: Psychosom. Med. *8*:36, 1946. (9) Jacobsen, E., and Skaarup, Y.: Acta pharmacol. et toxicol. *11*:117, 1955. (10) Jacobsen, E., and Skaarup, Y.: *ibid.*, p. 125. (11) Brady, J. V., in Cole, J. O., and Gerard, R. W.: Psychopharmacology: Problems in Evaluation, Washington, D. C., Nat. Acad. Sc.—Nat. Res. Council, pub. 583, 1959, pp. 46-63. (12) Skinner, B. F.: Science and Human Behavior, New York, Macmillan, 1953. (13) Skinner, B. F.: The Behavior of Organisms: An Experimental Analysis, New York, Appleton, 1938. (14) Brady, J. V., in Braceland, F. J.: The Effect of Pharmacologic Agents on the Nervous System, Baltimore, Williams & Wilkins, 1959, pp. 104-125. (15) Wikler, A.: The Relation of Psychiatry to Pharmacology, Baltimore, Williams & Wilkins, 1957, p. 216. (16) Brady, J. V.: Ann. New York Acad. Sc. *64*:632, 1956. (17) Dews, P. B.: Ann. New York Acad. Sc. *65*:268, 1956. (18) Skinner, B. F., in Cole, J. O., and Gerard, R. W.: *op. cit.*, ref. 11, p. 225.

investigative technics for localizing psychotropic agents' action sites

Several contrasting methods of investigation may be utilized to determine the sites of action of psychotropic drugs. They have not all been successful, but all are ingenious and many are promising. With the greatly expanded use of these agents, correlation between clinical observation and reproducible experimental results becomes advisable. In no other manner can a thorough understanding of the nature, mechanism and localization of drug action be obtained.

The precise neurophysiologic action of any drug can be learned only by utilization of animal experiments. Behavior and specific emotional responses may then be observed and a cause and effect correlation established. However, to apply such results directly to human responses may lead to serious errors. For this reason human subjects must also be employed whenever feasible, to avoid the possibility of mistakes incurred from reasoning by analogy.[1]

Pharmacologic study of a drug is an extensive field. Of necessity, it impinges on the corollaries of biochemistry, enzymology, pathology and endocrinology. This review, however, is concerned primarily with answers to these questions:

a. Is the drug action one of stimulation or depression?
b. Does its primary action involve the central or autonomic nervous system?
c. What behavior changes are induced by the drug's administration?
d. What side effects are evoked?
e. To what degree can animal results be transferred to humans?

SUMMARY OF INVESTIGATING TECHNIQUES

Animal	Human
1. Recording EEG waves from subcortical brain levels, before and after administration of the drug.[2]	1. A norm chart of the patient's behavior characteristics and body chemistry levels is established. It is important that the patient's age and sex, environment, responses to stress, hunger, fear and alcohol, his ability to perform mental tasks, his temperature, and the ease of inducing vomiting be considered. Behavior characteristics are compared after one dose, after a daily dosage for a short period, and after a long period.
2. Tests for protection afforded by the drug against circulating emetic agents.[3,4]	2. Comparison of cortical and subcortical stimulation effects on human behavior, before and after the drug is given orally or parenterally.[11]
3. Tests involving drug-induced behavior changes in special animal types, **e.g.**, certain fish.[5]	
4. Use of Siamese fighting fish to determine changes in behavior after living in water treated with the drug.[6]	
5. Use of radiolabeled drugs to determine their cerebral distribution and site of greatest concentration.[7-9]	
6. Chemical or surgical ablations of discrete brain segments; surgical excision of whole brain lobes.[10]	

RADIOACTIVE LABELING OF DRUGS

Drugs which have nervous system effect have been made radioactive and used to map the brain for general distribution and for sites of greatest concentration. For this purpose P^{32}, C^{14}, and S^{35} have been used most frequently and successfully.[7,8,9] The details of the technique and the purpose of the individual investigations may differ, but the essentials are very similar. Such experiments are primarily directed at determining the action site, and to a lesser extent the nature and degree of chemical changes induced in the central nervous system by drugs. Dogs,[7] mice[8] and rats[9] have been used as experimental subjects.

The technique requires that the radioactive substance be supplied at a rate sufficient to maintain the desired circulating concentration and that it enter neurons at a higher rate during induced neural activity, as by stimulation of one eye with a blinking light. The radioactive material is administered by injection. After a predetermined time the animal is sacrificed. Brain tissue from different levels, as well as blood and spinal fluid, is assayed for radioactivity. Brain sections are used for radioautographic negatives made on medical film of very fine grain; these will indicate the distribution and areas of greatest concentration of the radioactive material.

Urine, blood and spinal fluid are tested by paper chromatography to determine the nature and concentration of the metabolites formed.[8] Generally, drugs which have definite central nervous system effects will show the greatest radioactivity in the gray matter, the maximal concentration being in the limbic cortex and the hippocampal formation.[9]

Radioautograms of control rat brains sectioned after intraperitoneal injection of S^{35}-labeled l-methionine showed increased radioactivity in the subcortical hypothalamic nuclei, thalamic nuclei and the pituitary gland. Reserpine, when injected for several days prior to the administration of radiomethionine, selectively depressed the metabolism of subcortical brain areas (clinically evidenced by somnolence and inactivity).

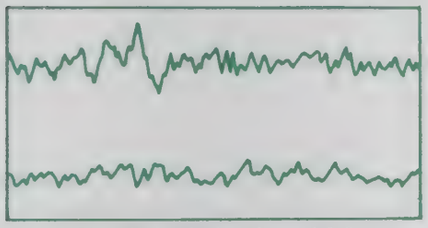
REFLECTION OF ELECTROCHEMICAL BRAIN CHANGES IN EEG

Electroencephalography is widely used in this type of investigation and is applicable to studies on both animals and human subjects. The results obtained in animals as an experimental means to determine the nature, the location or the duration of a drug's effect are reliable and reproducible. As in routine diagnostic electroencephalography, the wave patterns are evaluated for amplitude, rate, regularity and configuration. The EEG taken after the administration of a test drug, when compared with the basic pattern, will reveal the type of action and the area of greatest response. Delgado and Mihailović[2] carried this technique a step further. Using unanesthetized monkeys which had been prepared with permanently implanted wire electrodes (40) at different brain levels, they first obtained basic wave patterns. Graphs subsequently produced by selective stimulation of these electrodes later served as control patterns to furnish information as to the nature of electrochemical changes produced by the administration of test drugs. They were thus able to localize a drug's cerebral sites of action.

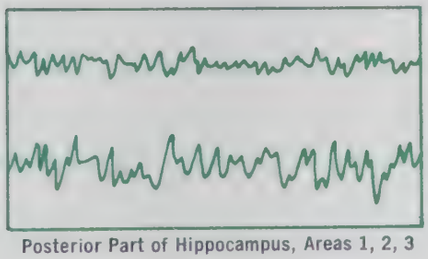
This work was not limited to observable motor effects and changed electrochemical brain activity as represented in EEG wave patterns. Unprovoked electrical activity of the brain and its modification by administered drugs were also subjected to this type of investigation.[2] Thalamic and limbic formation effects, as well as motor cortex effects, were obtained following administration of a tranquilizer drug.[2]

It was concluded[2] that the brain had many anatomical structures whose excitability and differing sensitivity to pharmacologic agents were useful means of testing these structures independently in drug-action studies. It was also apparent that more specific treatment may result from knowledge concerning the action of drugs upon different cerebral structures.

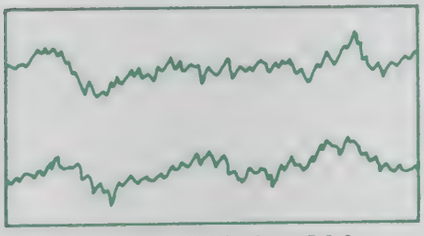
FIG. I. UNPROVOKED ELECTRICAL ACTIVITY OF THE MONKEY BRAIN. RIGHT MOTOR CORTEX; POSTERIOR HIPPOCAMPUS, AND LEFT SIDE OF THALAMUS.



Right Motor Cortex, Areas 4 & 6

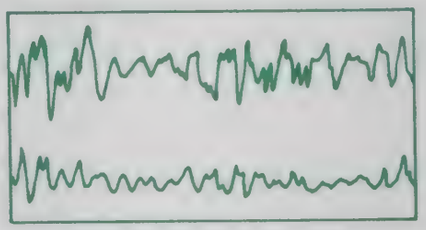


Posterior Part of Hippocampus, Areas 1, 2, 3

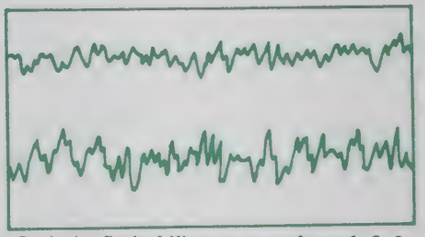


Thalamus, Left Side, Areas 5 & 6

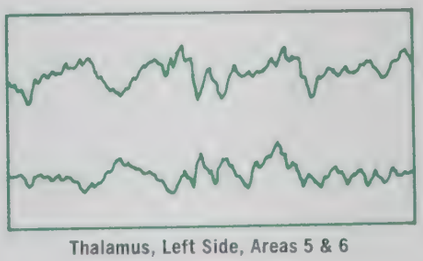
FIG. II. AFTER CHLORPROMAZINE. SLOWING OF FREQUENCY AND INCREASED AMPLITUDE IN MOTOR CORTEX; MODIFIED ACTIVITY OF POSTERIOR HIPPOCAMPUS AND THALAMUS.



Right Motor Cortex, Areas 4 & 6



Posterior Part of Hippocampus, Areas 1, 2, 3



Thalamus, Left Side, Areas 5 & 6

Adapted from Delgado and Mihailović[2]

ELECTRICAL INVESTIGATIONS OF BEHAVIOR

That limb and body movements could be induced and controlled by electrical stimulation of motor areas of the cerebral cortex has long been known and demonstrated. Delgado,[11] however, photographed cat motor cortex stimulation effects which could be induced independently of any emotional display; the animal's evoked posture was not associated with any sign of anger, hunger, etc. Similar experimental work with monkeys showed that electronic stimulation of the cortex while grooming a cage mate was not productive of any social activity change during an evoked head turning.

In addition, Delgado[11] has demonstrated that behavior could be influenced similarly by electrical stimulation of some areas in the subcortical brain. Hair-fine bundles of insulated wire were introduced into the animal brain; each target area was preselected in stereotaxic maps of the brain. The leads were brought to a small drill hole in the skull and cemented to the bone. As many as 42 contacts were implanted into a single brain. The social activity effect of brain stimulation was then recorded on 16 mm. motion picture film utilizing a time-lapse mechanism taking from 4,000 to 20,000 pictures daily.

Correlation of physiologic, psychologic, and sociologic effects indicated no disturbance of social activity during motor cortex stimulation. Similarly, emotional behavior responses have been evoked by electrical stimulation of discrete brain areas with this technique. For example, cats were utilized to demonstrate true rage by several stimulations of the amygdaloid nucleus. Cats and monkeys were tamed during caudate nucleus stimulation, reverting to their normal ferocity when stimulation was stopped. Stimulation of the monkey septal area caused loss of aggressiveness. By stimulating the tectum and lateral thalamus, cats were motivated to learn a means of preventing brain stimulation.

Delgado's work[11] demonstrates that electrical stimulation of the human brain will also evoke behavior changes; these are specific and reliably reproducible. By implanting fine electrodes in the brain of epileptics, schizophrenics and other patients, he was able to study the results of localized brain stimulations. Conversations were tape-recorded while simultaneous electroencephalographic records and stimulation signals were made.

In his experiments,[11] frontal lobe stimulation evoked blocking of thought. In one subject, recitation of poetry stopped abruptly during stimulation. Questioned later, he said he had a peculiar sensation in his head and could not think of the words. "My mind was blank, as if I had drunk a lot of beer," was his explanation. Stimulation of other areas failed to produce this effect. In another patient, stimulation of the inferolateral surface of the frontal lobe produced a significant increase of the amount of talking and in the frequency of friendly remarks. This same male patient when stimulated at the superior temporal convolution produced the appearance of feminine striving together with confusion about his own sex.

This 11-year-old boy said, "I was thinking whether I was a boy or a girl, which one I'd like to be," and, "I'd like to be a girl." After another stimulation this patient expressed a wish to marry the male interviewer. Stimulation of this same area in an adult female was followed by discussion of marriage and expression of a wish to marry the therapist.

Temporal lobe stimulation of another patient evoked declarations of pleasure accompanied by giggles and joking. Frontal lobe stimulation caused fear, accompanied by an expression of anxiety and declaration of feeling an imminent threat of unknown nature.

All these evoked effects were apparently spontaneous. The subjects did not feel impelled to make them. Delgado states: "Electricity influences the neurons, can direct the brain to produce movements, hallucinations, drives, emotions, hostility, and friendliness, and is even able to modify human thoughts."[11]

Such results have obvious application in the future to the evaluation of a drug's influence on the physiologic activity of discrete brain areas, since a specific alteration of behavior after medication may be indicative of drug effect on that segment of the brain implicated by the electrical stimulation experiments.

SPECIAL ANIMAL TYPE TESTING

Cutting and others[5] noted that fish may be suitable for studying the effects of, and even the bio-assay of drugs that influence the central nervous system. More than one variety of fish was utilized in their experiments. The characteristic behavior in the presence of certain drugs was found to be predictable; when challenged with a stress situation the response served as a measure of the action and efficacy of a drug. Modification of species behavior has been elicited by a wide variety of drugs. The best example of this is the apparent docility of the Siamese fighting fish following the administration of chlorpromazine. They concluded: "Ataraxics, sedatives, stimulants, and autonomic drugs produced in fish counterpart reactions to those observed in mice and higher animals. In some instances it was possible to observe characteristic differences between drugs of the same pharmacological type." Using the Siamese fighting fish, Abramson and Evans[6] also reported characteristic behavior changes following the administration of LSD 25.

Localizing drug action with the aid of these observations is predicated on a correlation between human or other mammal behavior with those of several varieties of fish. When a drug is found to evoke similar behavior changes in cats, for example, it may reasonably be assumed that the action site is the same in both. Fish experiments may serve particularly to corroborate findings from other animal investigations which specifically localize a site of drug action.

Antiemetic Effects as an Aid to Localization—The antiemetic efficacy of a drug is to a great extent dependent upon the site in the nervous system affected by the drug. The manner in which nausea is induced for experimental purposes is the deciding factor. Using dogs and intravenous emetic agents, Brand and associates[3] postulated that chlorpromazine produced its antiemetic action by a selective depression of the medullary chemoceptive emetic trigger zone (CETZ). Wang,[4] whose hypothesis of competitive binding of receptor sites in the trigger zone by circulating emetic and antiemetic agents is generally accepted, believes that the existence of such a CETZ in the *area postrema* explains the mechanism of antiemetic action displayed by some drugs. Since many

phenothiazines, including TRILAFON (perphenazine), have significant antiemetic benefits, it would be entirely reasonable to assume that one of their sites of action is this same *area postrema* where they successfully bind the receptor sites.

ABLATION PROCEDURES

The behavior changes resulting from surgical ablation of circumscribed cerebral areas have also served to confirm presumed functions of these areas. Pribram and Bagshaw[12] performed bilateral ablation of the frontotemporal region in wild animals, changing them into tame and docile creatures. They lost their fear, subjected themselves repeatedly to the same harmful situation and displayed dietary habits which were contrary to those of the untreated animal. Exaggerated and unnatural sexuality, bizarre in nature, became evident. Somewhat similar behavior was noted in monkeys when the caudate nucleus was electrically stimulated. Lobectomy, a more extensive procedure, has effectively evoked personality and behavior changes. Chemical ablation studies have been performed,[10] using hollow needles introduced by stereotaxic guides, on all levels of the brain. Behavior inhibition and stimulation were noted, depending on the type of drug introduced.

Ablation studies have had their most frequent application in studies oriented to learning the observable effects of excising discrete subcortical brain segments in animals. Despite utilization of microscopic dissecting techniques, this is a relatively inaccurate procedure.[7] A more basic and infinitely more precise investigatory tool, microscopic enzymology, has identified at least seven enzymes in individual neuronal cells.[13] It is hoped that concerted ablation-chemical studies may furnish highly significant information which may guide our evaluation of localized drug action in the nervous system.

ELECTRON MICROSCOPY

Examination of specially processed ultrathin sections affords the investigator an "...approximation to the activities of the living state of nerve protoplasm."[13] The extremely intricate functions of the brain and the coordinated, yet rapid, sequence of its processes make the most powerful light microscope inadequate for the accumulation of knowledge of the fine structure of nervous tissue. Electron microscopy makes it possible to undertake a systemic study of nervous tissue. It reveals "...differentiated new structural patterns which may extend from the cellular level to macromolecular dimensions."[13] As is so often the case with new investigative techniques, the true significance of many of the new structural patterns is not yet understood. However, the increased morphologic differentiation probably will supply the neurophysiologist and biochemist with more accurate criteria for submicroscopic investigation.[13]

The greater availability of and increased familiarity with the use of the electron microscope will afford investigators a research modality of considerable value. Hitherto invisible submicroscopic morphologic changes become subject to detailed study; appreciation of their significance and association with disturbed behavior may result in a structural understanding of mental diseases.

In an analogous manner, ultracellular changes induced by drug therapy may be investigated with the goal of localizing the site and mechanism of activity. This type of research is in progress but conclusions are not yet clear-cut. The basic processes involved and methods of influencing them are still being explored.

Polarized light analysis, x-ray diffraction and x-ray microfluorescence, microwave spectroscopy, and nuclear magnetic resonance spectrometry may also supply additional and accurate methods for other specialized microscopic investigations.[13] Such refinements in tissue examination techniques may ultimately be of great aid in the demonstration of the effects of psychotropic drugs, thus pinpointing their sites of action.

ENZYME ACTIVITY STUDIES[13,14]

Produced by living cells but acting independently of them, enzymes affect other biochemical reactions. The precise mechanism of enzyme action is still unknown, but is accepted as being entirely chemical. Action is specific in that enzymes act only on certain substances, and that they are destroyed during their reactivity.[14] Coenzymes are stable organic compounds which are necessary for the functioning of enzymes. Although usually separable from the enzyme, they are most frequently associated with the enzyme they activate.

Investigation of enzyme systems in brain function studies requires precise and accurate qualitative and quantitative methods for identification and assay. Since this is a highly complex technical field, utilizing microchemical procedures, details will be omitted. It is essential, however, to recognize that this rapidly developing field has great significance in the understanding of the basic mechanism of nervous system metabolism.

Cellular respiration which is the *sine qua non* of all tissue function is dependent on enzyme action. The isolation of coenzymes and the investigations on them have supplied a great deal of information on carbohydrate metabolism and cellular respiration.

Variations in enzyme identity, local brain concentration, localization, hydrogen-ion concentration of substrate and the changes produced by pathologic states appear to be of great significance for an understanding of the fundamental nature of brain function.[13]

Unfortunately, only little clinical application of this information has yet been possible. The significance of brain enzymes and coenzymes in the mapping of brain areas for ataractic and other psychotropic drugs is just beginning to be explored. The connection of the monoamine oxidase inhibitors with depressed states is a significant step in this direction.

It is now generally accepted that acceleration of the catalytic action of the enzyme monoamine oxidase in the brain is at times associated with the clinical development of depressed emotional states. A group of chemical agents which are presumed to retard or inhibit this acceleration, either by changing the hydrogen-ion concentration of the thalamic brain or by inactivating the coenzyme

associated with monoamine oxidase, has been used to treat this psychiatric aberration; clinical results frequently have been very gratifying.

HORMONES AND ACTION-SITE LOCALIZATION

The response to a drug administered for a specific purpose may depend entirely upon the drug's pharmacologic effect on target tissues or organs. However, it may owe its value in great part to a hormone action. Thus, it may release stored hormone, accelerate the formation of hormone, or inhibit hormone effect. Certain side effects during drug therapy may become understandable on this basis.

Generally, circulating hormone may be said to affect all body tissues. Some hormones manifest their effect mainly in localized areas.[16] The methods for investigating hormone-drug effects on nervous tissue are predicated on the concept that in health the endocrine system functions as a balanced system. "No single hormone or endocrine gland acts wholly by itself at any time...."[16] Endocrine gland effects are produced by a fluctuating interplay of several. Functional or pathologic variations in any one of the glands will be reflected in compensatory changes in some of the others to re-establish the disturbed equilibrium or to create an effect. Any drug which is expected to have a hormonal effect must be followed by quantitative determinations of endocrine secretions (natural, or as metabolic products), metabolic rate, fluid-electrolyte balance, etc., since hormones do not exert their influence at their sites of production.

Methods of investigation:[16]

a. chemical or biological assay of the amount of hormone or of its metabolites present in the blood or urine is a useful method for following the compensatory responses of the endocrine glands to an administered drug

b. operative removal of a gland from a mature animal, and then following its responses to drugs or replacement hormones

c. administration of modifying drugs to patients with hypo- or hyperfunction of an endocrine gland

The mechanism by which hormones produce their effect is unknown. It has been established that they do not initiate new biochemical reactions, but they do mediate the rate and intensity of established reactions and may reasonably be said to act like catalytic agents.[15] Hormones regulate virtually all life processes and must influence enzyme reactions in some way—but no such effect has yet been demonstrated in test-tube experiments.[14]

Clinical or experimental application of these principles may lead to more detailed information on the influence of an administered therapeutic agent on the endocrine ensemble and so, indirectly, on the central nervous system metabolism.[16] Variations in nervous system metabolic activity will result in local chemical changes[13] manifested as emotional or behavior variations; their nature will furnish clues to localize the site of drug action.

sites of action of phenothiazines

Although the phenothiazines differ considerably in activity and have widespread action in the body, their action is primarily on three neuroanatomic systems: the hypothalamus; the reticular system of the medulla, mid-brain, and diencephalon; the limbic system, particularly the amygdaloid and hippocampal segments.[17]

This localization of the sites of phenothiazine action is based on:[17]

(a) the antiemetic effect of these drugs, implying medullary reticular depression

(b) barbiturate potentiation and sedation, suggesting an effect on the mesencephalic reticular system and the hypothalamus

(c) endocrine and autonomic effects which indicate that the hypothalamus is the chemoreceptor site

(d) extrapyramidal effects which point to the limbic system

The weaker phenothiazines exert their greatest depressing effect on the hypothalamus and on parts of the reticular system and have less effect on the limbic system. Clinically this is demonstrated by the relatively higher incidence of sedative and autonomic-endocrine responses as compared to the low incidence of extrapyramidal system effects.[17]

The more potent phenothiazines exert greater effect on the limbic system, as is suggested by their greater propensity to cause extrapyramidal signs. Less effect is noted on the hypothalamic and reticular systems, as is evidenced by the lack of drowsiness, autonomic-endocrine symptoms and lessened drug potentiation.[17]

This classification "...implies that the clinical effects of each drug are attributable to selective affinity for sites in various sub-cortical areas."[17] This selectivity may be determined by the halogen associated with the phenothiazine ring and the structure of the side chain.

Bibliography: (1) Lehmann, H. E., in Braceland, F. J.: The Effect of Pharmacological Agents on the Nervous System, Baltimore, Williams & Wilkins, 1959, p. 128. (2) Delgado, J. M. R., and Mihailovic, L.: Ann. New York Acad. Sc. *64*:644, 1956. (3) Brand, E. D.; Harris, T. D.; Borison, H. L., and Goodman, L. S.: J. Pharmacol. & Exper. Therap. *110*:86, 1954. (4) Wang, S. C.: J. Pharmacol. & Exper. Therap. *123*:306, 1958. (5) Cutting, W.; Baslow, M.; Read, D., and Furst, A.: J. Clin. & Exper. Psychopath. *20*:26, 1959. (6) Abramson, H. A., and Evans, L. T.: Science *120*:990, 1954. (7) John, E. R.: J. Neuropath. & Exper. Neurol. *15*:103, 1956. (8) Goldenthal, E. I.; Nadkarni, M. V., and Smith, P. K.: J. Pharmacol. & Exper. Therap. *122*:431, 1958. (9) Flanigan, S.; Gabrieli, E. R., and MacLean, P. D.: A.M.A. Arch. Neurol. & Psychiat. *77*:588, 1957. (10) MacLean, P. D.: J. Nerv. & Ment. Dis. *127*:1, 1958. (11) Delgado, J. M. R.: Tr. New York Acad. Sc. *21*:689, 1959. (12) Pribram, K. H., and Bagshaw, M., cited by MacLean, P. D.: *ibid.* (ref. 10). (13) Richter, D., *et al.*: Metabolism of the Nervous System, New York, Pergamon Press, 1957, pp. 1-3, 26, 27, 50, 51, 323-328. (14) Kleiner, I. S., and Orten, J. M.: Human Biochemistry, ed. 5, St. Louis, Mosby, 1958, pp. 225-238. (15) Williams, R. H.: Textbook of Endocrinology, ed. 2, Philadelphia, Saunders, 1955, pp. 2, 3, 8, 10. (16) Wiggers, C. J.: Physiology in Health and Disease, ed. 5, Philadelphia, Lea & Febiger, 1950, pp. 1106-1112. (17) Ayd, F. J., Jr.: J. M. Soc. New Jersey *57*:4, 1960.

contributions of neurophysiological animal preparations

The utilization of animal preparations for observation and interpretation of central nervous system function and for explanation of pharmacologic action is absolutely essential. If the ultimate quest of science is the "nature of man,"[1-3] then one is strongly tempted to add as a corollary—and largely through the nature of animals. This review is undertaken to present more comprehensively the specific contributions of animal preparations—both classical and more recent—to present-day knowledge of brain function.

Since antiquity the concept of a brain has been given representation in various organs of the body. In antiquity the formulated concept most favorable to the nervous system considered a vegetative soul in the lumbosacral cord which subserved appetite; the emotions, or animal soul, was next higher in the cervicothoracic area; and reason, which was subserved by the immortal soul, resided fittingly within the brain—the highest seat.[4] Classical neuraxial transections of animals did much to lift this veil. Today the physiologist hopes that the experimental findings which he has painstakingly accumulated will permit interpretation of all behavior in terms of physicochemical activities in the neuronal network.[5]

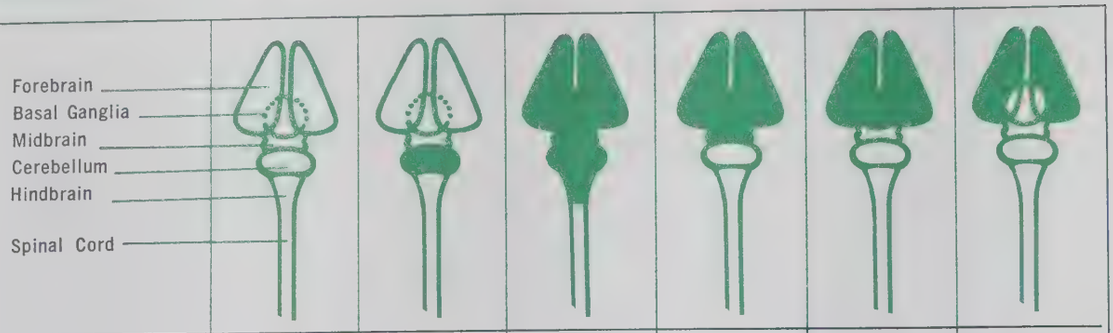
THE "CLASSICAL" EXPERIMENTAL PREPARATIONS

In contrast to the discrete brain area preparations which more refined techniques afford today, "classical" neurophysiological animal preparations were transections done at various levels of the neuraxis. Although early preparations were largely crude by present-day standards, they permitted the observations which suggested a functional organization within the brain. These preparations (extirpated areas in black) are diagrammatically illustrated in Fig. 1 together with a summary of the experimental observations in arbitrarily chosen categories of behavior.[6] The plus sign (+) indicates normal function, ++ increased, +++ greatly increased, while the minus sign (–) indicates absence of function.

SPINAL PREPARATION

This preparation must be kept alive with a bellows since automatic respiration, as all complex behavior, is lost.[6] Reflexes are short and hyperactive. This type of preparation offers the simplest situation for studying competition which occurs between reflexes. At this segmental level there is already evidence of the check and countercheck "servo-mechanisms" that are more complex at higher levels; at this level they act to make movements smooth and to steady maintained contractions.[3] Cobb[6] considers that the spread of these impulses, making associations at different segmental levels, furnishes a clue to the nature of "mental" attributes of memory and learning.

FIG. 1 SUMMARY OF EXPERIMENTAL INVESTIGATIONS OF MOTOR INTEGRATION IN MAMMALIAN PREPARATIONS



Functions	Normal	Decerebellate	Spinal	Hindbrain	Midbrain	Hypothalamic
Initiative	+	+	–	–	–	–
Conditioned Reflexes	+	+	–	–	–	–
Emotional Reflexes	+	+	–	–	–	+++
Locomotor Reflexes	+	Incoordinate	–	–	+	++
Righting Reflexes	+	Incoordinate	–	–	++	+
Anti-Gravity Reflexes	+	Incoordinate	+	+++	++	++
Respirations	+		–	+	+	+
Neck Reflexes	+	+	–	++	+	+
Spinal Reflexes	+	+	++	++	++	++

Adapted from Cobb, S.[6]

DECEREBRATE ANIMAL

Decerebration may be performed by transection of the brain stem between the vestibular nuclei and anterior colliculi or by tying the common carotids and basilar artery at the center of the pons so as to deprive the forebrain of its blood supply.[7] The result in a cat is the characteristic decerebrate stance, rigid to exaggeration, the head and tail upraised.[6] Minor pseudoaffective reactions have been reported. These observations suggested the existence of higher regulatory centers, dissociated by the transection.

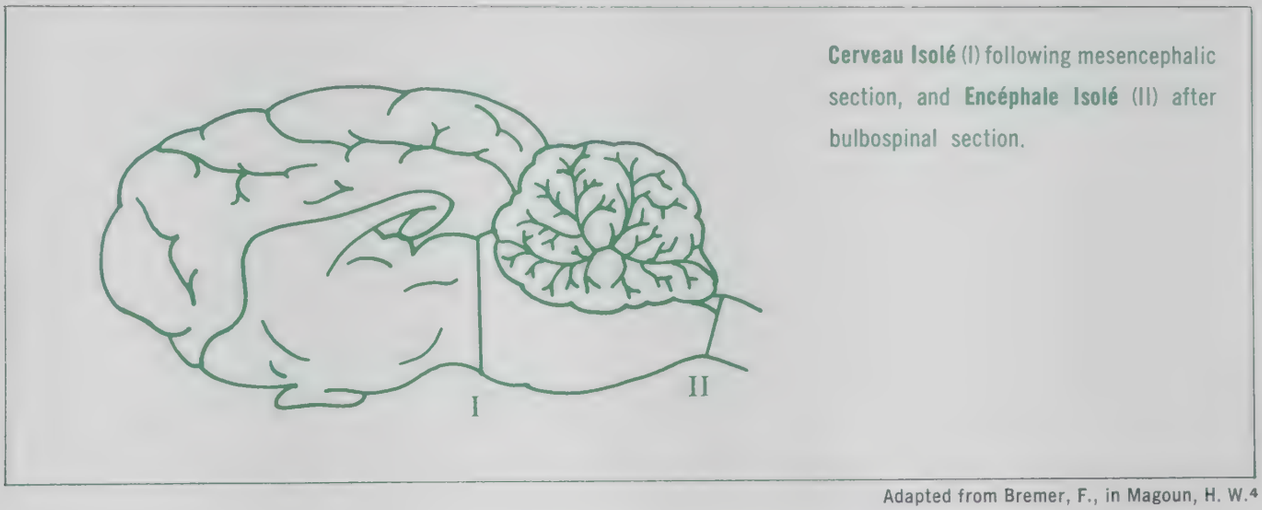
CERVEAU ISOLÉ—ENCÉPHALE ISOLÉ

It was the study of the isolated brain and nervous system of animals and the recognition of electric activity within these preparations that ultimately pointed the way to the dramatic discovery that the brain of the undisturbed human exhibits waves of electric potential.[8]

Although the spinal and decerebrate animal had long been studied, the former since antiquity, attention had always been directed, primarily, to activities caudal to the transection. Bremer,[9] studying

electric activity ahead of (cephalad to) the cut, recognized the waking pattern of cerebral activity following a bulbospinal section (*encéphale isolé*), as contrasted to the sleep pattern seen subsequent to section at midbrain level (*cerveau isolé*). His observations have contributed greatly to our present concepts of wakefulness,[4] attention and arousal. Thus, "...the coma of *cerveau isolé* animals was shown to depend upon exclusion from higher structures of 'activating' stimuli conducted selectively through this median zone [reticular formation] rather than upon the blockade of primary sensory signals transported to the cortex through the lateral brain stem."[10]

FIG. 2 SECTIONS OF CAT BRAIN



Cerveau Isolé (I) following mesencephalic section, and **Encéphale Isolé** (II) after bulbospinal section.

Adapted from Bremer, F., in Magoun, H. W.[4]

Within recent times the concept of consciousness, more particularly in relation to the reticular activating system, has become of increasing significance in neuropsychiatric thinking.[10] Data obtained largely from experimental animals are supplying the information as to the origin, distribution, topography and physiology of the reticular formation.[11]

THE DECEREBELLATE ANIMAL

Until descriptions of altered behavior following removal of the animal cerebellum were obtained, functions attributed to this area were merely speculative.[12] Willis, for instance, had assumed that the cerebellum controlled heart beat, respiration and other vegetative functions.[13] The broad outlines of cerebellar influence in control of motor activities were laid down by studies of decerebellate preparations. Validity of results has improved with refinement of technique, though surgical and experimental difficulties have not been entirely overcome.

The decerebellate preparation at rest appears almost normal but lack of coordination makes the animal helpless to carry out a motor act.[6] Most of the responses studied are superimposed on a background of unanesthetized decerebrate rigidity, since anesthesia depresses cerebellar response. "In spite of the bias introduced through the use of decerebrate preparation in so much of this work, it nevertheless remains clear that cerebellar activities are principally related to the adjustment of

tonus of striated muscle."[12] The cerebellum influences electrical activity in the cerebral cortex. In man, one aspect of the cerebello-cortex relationship is the suggestion that "... asthenia is a manifestation of the withdrawal of tonic facilitatory action exerted on the cerebral cortex by the cerebellum."[12]

A considerable mass of information on the cerebellum is now available. The exact nature of cerebellar regulation, however, and its *raison d'être,* still escape the investigator.[5] Deficits following ablation are too complex; real understanding may be anticipated when the motor neuron control system is tested by more sophisticated means, both in the presence and absence of cerebellar function.

MIDBRAIN PREPARATION

A typical midbrain preparation is separated from the upper basal ganglia and cerebral hemispheres. It has no memory, and emotional responses are absent.[6] Nuclei at this level are so close that transection by the experimenter's knife lacks accuracy. In addition, division between fore- and midbrain has been arbitrary. The functional interrelations of gait, such as walking, running, jumping, have not been elucidated by ablation experiments.[6]

Animal preparations maintain spasticity until caudal sequential transections of the brain stem reach the region of the vestibular nuclei.[10] Orthodox concepts attributed the spasticity to vestibulospinal activity until later experimentation and study revealed that the reticular formation, also transected at this level, is closely associated with postural formation.

HYPOTHALAMIC PREPARATION

Animals with only the hypothalamus and some adjacent structures remaining above midbrain are almost entirely devoid of memory and do not benefit from experience.[6] The hypothalamus has come to be looked upon as the "center" of emotion.[15] Thus, these animals overreact to all stimuli, whether irritating or pleasurable.[6] A hypothalamic cat, for instance, "... will become as vicious and aggressive as the shrew...."[14] More recent findings indicate that while "... the hypothalamus serves as an integrator of emotional expression, it contributes only indirectly to the experience of emotion."[15] Papez includes the hypothalamus as one of the structures of the visceral brain.[16]

DECORTICATE ANIMAL

Since cortical development, or encephalization, has reached its peak in man, transfer of experimental observations from decorticate animals to man is not satisfactory. To some extent, knowledge of cortical function has been obtained from anencephalic infants and decorticate patients. By comparison with lower animal forms, neurophysiologists[17] have recognized the importance of the human cortex as the origin of spontaneous activity, the site of conditioned reflexes, memory, intelligence, and consciousness.

Though decorticated, the carnivores, such as the dog and cat, can still walk and run in almost normal fashion.[18] The well-developed cortices of these animals are functionally less important than

the cortex in primates (monkeys, apes and man). It has been shown that in the evolution of the primate there is increasing importance of the cerebral cortex with greater localization in this area of essential functions.

newer specialized CNS preparations

Development of greater skill in neurosurgical and testing techniques has improved the investigator's ability to measure the mental processes themselves—ideas, attitudes, and thoughts. Thus, ablation procedures involving more selective, or discrete, areas in the monkey brain have made the primate an important research tool in studying relationships between the cerebral mantle and mental processes, i.e., the "mind-body"[19] relationship.

THE MIND-BODY RELATIONSHIP

Although not universally believed, many investigators consider the mind a function of the brain in action or, as stated by Herrick, "... structure is behavior in instantaneous photograph."[20] The interaction of mind and body, as presented by Sherrington[21] in "The Integrative Action of the Nervous System," may be further illustrated. In viewing an object, the photochemical reaction traveling from retina to pupillary activating fibers and to brain cortical areas is physical, but the innumerable coincident visual impressions are a "psychical" event.[19] These latter events may now be explored by neurobehavioral techniques incorporating the specialized ablative procedures.

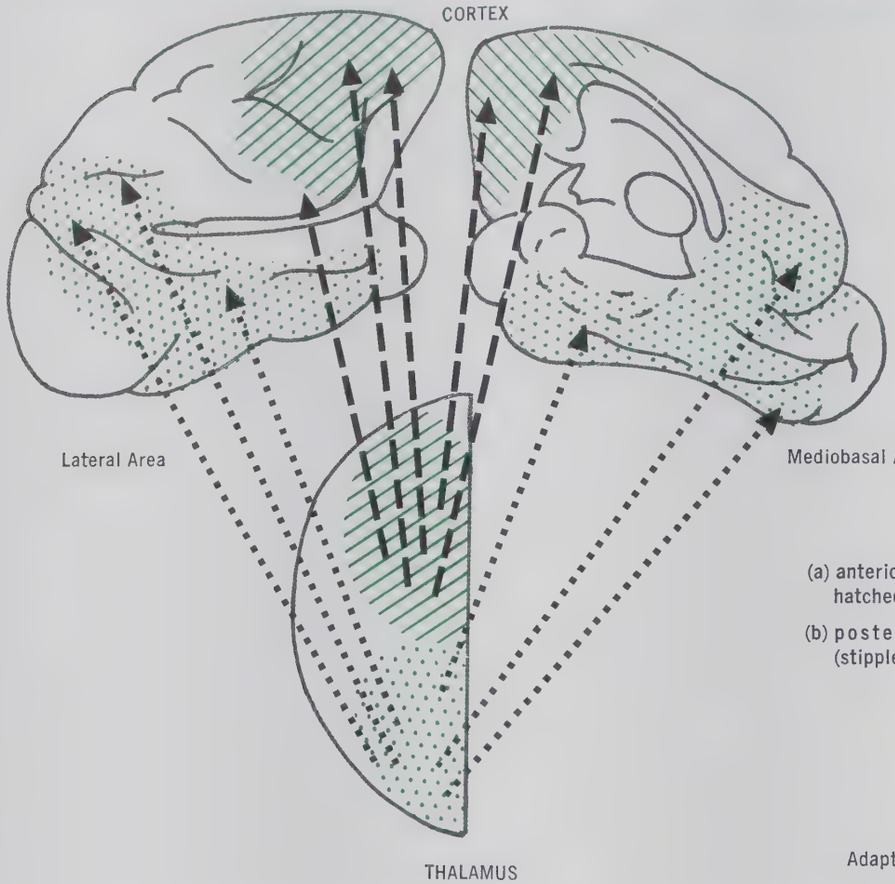
A NEUROBEHAVIORAL EXPERIMENT IN MONKEYS

Investigations with the newer experimental techniques present evidence of an area within the primate forebrain especially related to problem solving. Evidence also suggests a neurophysiological basis for two different classes of behavior even in this area, intentional and differentiative.[19] As an example of the application of these newer techniques, a brief outline of experimental method and observations supporting this inference is presented here.

The anatomical areas involved are the thalamus and cortex. The thalamic subdivisions together with the corresponding cortical projection fibers may conveniently be differentiated into the anterior (frontal) intrinsic system and the posterior intrinsic system of the forebrain (Fig. 3). Following bilateral resections of each of these areas separately, behavioral tests are performed on rhesus monkeys and results compared with normal controls.[19]

Stated generally, the test problem involves the strategy of moving several objects until a peanut is found under one (Fig. 4). The peanut remains under the same object, although the objects are constantly shifted in position, until the criterion of five consecutive successful attempts is achieved by the monkey. Another object is then added, and the process repeated, until a total of 12 is reached.[19]

FIG. 3 SCHEMATIC REPRESENTATION OF THE THALAMOCORTICAL RELATIONS IN A MONKEY

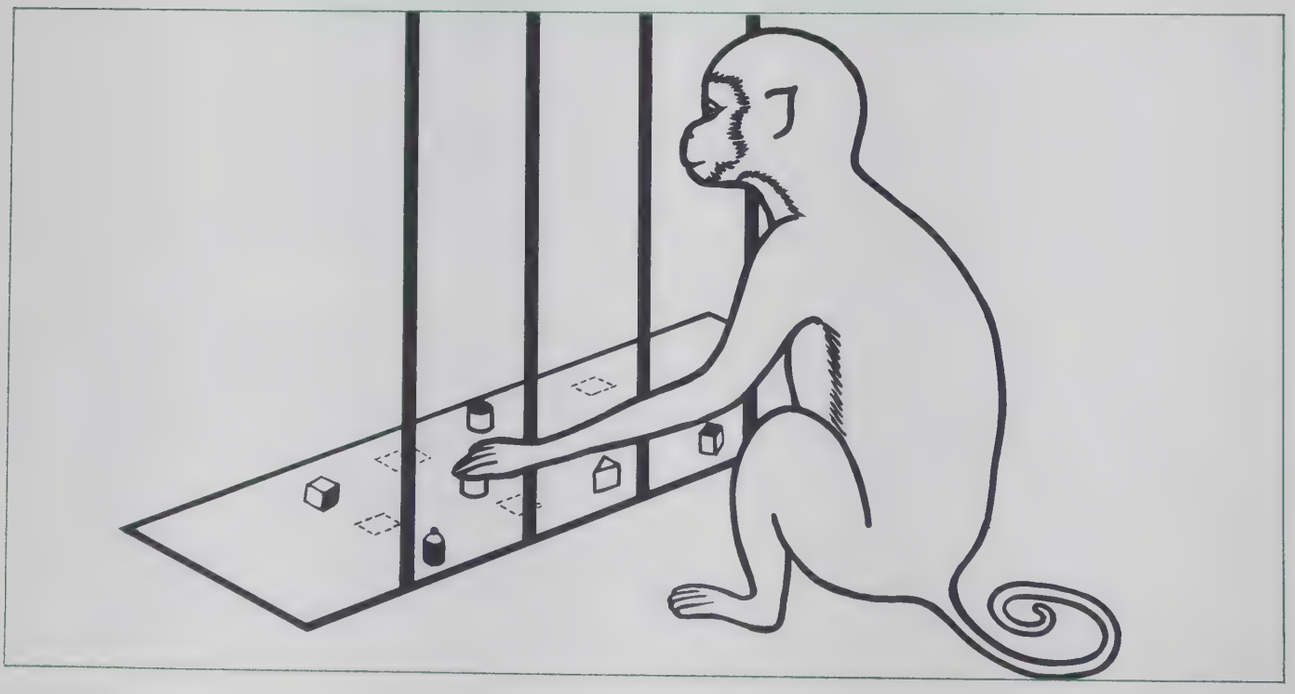


(a) anterior intrinsic system (cross-hatched area and broken lines)

(b) posterior intrinsic system (stippled area and dotted lines)

Adapted from Pribram, K. H.[19]

FIG. 4 A PLACEMENT OF OBJECTS IN NEUROBEHAVIORAL EXPERIMENT ON MONKEYS



Adapted from Pribram, K. H.[19]

Results suggest that posterior lesions affect the delineation of the problem (searching for the peanut), whereas anterior lesions interfere with intentional behavior (selecting object under which peanut was found previously).[19] Denny-Brown,[24] by comparable experimental techniques, has distinguished between cortical resections that affect patterns of avoiding (withdrawing) and those that affect patterns of approaching (placing, grasping, hopping). These data imply that neural mechanisms are "...important determinants of moment-to-moment behavior..."[19] which are limited, within a matrix set by other events, as proposed by Freud[22] and Forgus.[23]

ANIMAL STUDY AND CLINICAL PATTERNS

In relating problems of mind and behavior to neural mechanisms, neurophysiology, with its access to animal experimentation, has been admirably suited to make contributions to psychological research.[15] Orbital leucotomy, first experimentally performed on cats, was later to be performed on man. Later experimental studies led to the introduction of frontal lobotomy. Some aspects of this experimental work, reported in previous studies in this series, will be briefly reviewed here.

Stereotaxic methods which permit discretely selective stimulation of the animal brain underscore the role of the rhinencephalon (or the philogenetically old cortex) in "...the orientation of behavioral patterns and in the control of emotional tension."[5] Induced lesions of the limbic system, separately and in combination, provide a continuing source of information.[25,26] "Experimental or pathological stimulation of these structures, particularly of the nuclei of the amygdaloid complex, results in striking changes in overt behavior and mental state both in animals and man."[5] Frequently, the experimental animal sheds light on the genesis of clinical states. An instance is the production of chronic peptic ulcers in normally behaving monkeys following prolonged stimulation of the hypothalamus,[27] and another is the significant findings in regard to psychomotor epilepsy and catatonic manifestations, derived from studies of hippocampal seizures in animals.[28]

animal versus human brain

LIMITATIONS AND CONTRIBUTIONS OF ANIMAL PREPARATIONS

In evaluating negative results from animal experiments, prudence is always necessary.[5] The specialized skilled "voluntary" movements of man, such as the fingers, tongue, lips and jaw, cannot be studied in other mammals. Nor can the most careful monkey experiments be accepted as completely applicable to man, in whom the motor subtlety of facial expression, of speech and dexterity are unique to the species.[6] Animal preparations, for instance, cannot be expected to reveal the importance of the cerebellum in coordinating speech. In psychosomatic studies,[29] it is self-evident that, although one may study the social behavior of a monkey, by no means can the psychiatrist know the psychic reaction within the animal.

As of now,[6] animal studies indicate no fundamental difference between "mental" and "nonmental" functions of the CNS except that the phenomenon of consciousness is more prominent as one ascends the phylogenetic scale. If any distinction may be drawn between man and lower mammals it is that the former generally acts in the light of past experience, whereas in apes "putting two and two together" is still a rudimentary process.[6]

ANIMAL PREPARATIONS IN THERAPEUTIC EVALUATION

As advances in psychosurgery and psychopharmacology increase the importance of neurology in psychiatric practice,[30] animal preparations play an increasingly important role in the analysis of the site or sites of drug action.[31] "Data from a single screening technique have often been interpreted as indicating a specific action on a certain level of the nervous system, apparently disregarding... possible effects at other levels of nervous system organization."[31] By sectioning the spinal cord of a cat, for instance, investigators have been able to study the influence of psychotherapeutic agents on areas other than the brain. Chlorpromazine and serotonin both depress cat spinal reflex activity, the site of action of chlorpromazine being on the presynaptic fibers of the cord.[31] Epilepsy affords an illustration wherein appropriately prepared animals may be utilized for expediting the testing of new agents as to their applicability to the cellular abnormality responsible for this disorder.[27]

CONCLUSION

Our knowledge and perception of brain function derived from animal study present the challenging problem that "...a few extra ounces of nerve cells and connections in the cortex have permitted symbolism in language and number and abstract reasoning to a degree so beyond that of other animals that something almost qualitatively new has been added."[8]

These experimental animal observations have aided the conceptual development of the nervous system "...as a progressive superimposition upon the segmental reflex arcs of circuits of increasing complexity, all of which originate in peripheral sensory mechanisms and end in motor or secretory effectors."[5] The correlated data of the combined disciplines of the physicist, the physiologist, the neuroanatomist, the psychiatrist and the psychologist are slowly narrowing the hiatus between mind and brain.

Bibliography: (1) Schrödinger, E.: Science and Humanism: Physics in Our Time, London, Cambridge, 1951, cited in Eccles, J. C.: The Neurophysiological Basis of the Mind, London, Oxford, 1953, p. 286. (2) Sherrington, C. S.: Man: On His Nature, ed. 2, London, Cambridge, 1951, cited in Eccles, J. C.: The Neurophysiological Basis of the Mind, London, Oxford, 1953, p. 286. (3) Eccles, J. C.: The Neurophysiological Basis of the Mind, London, Oxford, 1953. (4) Magoun, H. W.: The Waking Brain, Springfield, Ill., Thomas, 1958. (5) Bremer, F., in Field, J.: Handbook of Physiology, Section 1: Neurophysiology, vol. 2, Washington, D. C., American Physiological Society, 1960, pp. 1241-1243. (6) Cobb, S.: Foundations of Neuropsychiatry, ed. 6, Baltimore, Williams & Wilkins, 1958. (7) Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 6, Baltimore, Williams & Wilkins, 1955, pp. 960-985. (8) Gerard, R. W.: Am. J. Psychiat. *106*:161, 1949. (9) Bremer, F., cited in Magoun, H. W.: The Waking Brain, Springfield, Ill., Thomas, 1958, pp. 66, 67. (10) French, J. D., in Field, J.: Handbook of Physiology, Section 1: Neurophysiology, vol. 2, Washington, D. C., American Physiological Society, 1960, pp. 1281-1305. (11)

Jasper, H. H., *et al.:* Reticular Formation of the Brain, Boston, Little, 1958. (12) Brookhart, J. M., in Field, J.: Handbook of Physiology, Section 1: Neurophysiology, vol. 2, Washington, D. C., American Physiological Society, 1960, pp. 1245-1280. (13) Willis, T., cited in Brookhart, J. M.: *ibid.,* p. 1246. (14) Gerard, R. W., in Arieti, S.: American Handbook of Psychiatry, vol. 2, New York, Basic Books, 1959, pp. 1620-1638. (15) MacLean, P. D.: Am. J. Med. *25*:611, 1958. (16) Papez, J. W., in Jasper, H. H., *et al.:* Reticular Formation of the Brain, Boston, Little, 1958, pp. 591-605. (17) Main, R. J., and Richardson, A. W.: Physiology, ed. 2, St. Louis, Mosby, 1953, pp. 381-403. (18) Grinker, R. R., and Bucy, P. C.: Neurology, ed. 4, Springfield, Ill., Thomas, 1949, pp. 332-394. (19) Pribram, K. H., in Field, J.: Handbook of Physiology, Section 1: Neurophysiology, vol. 2, Washington, D. C., American Physiological Society, 1960, pp. 1323-1344. (20) Herrick, C. J., cited in Arieti, S.: American Handbook of Psychiatry, vol. 2, New York, Basic Books, 1959, p. 1640, footnote. (21) Sherrington, C. S., cited in Pribram, K. H.: *op. cit.* (ref. 19), p. 1324. (22) Freud, S., cited in Pribram, K. H.: *op. cit.* (ref. 19), p. 1340. (23) Forgus, R. H., cited in Pribram, K. H.: *op. cit.* (ref. 19), p. 1340. (24) Denny-Brown, D.: North Carolina M. J. *17*:295, 1956. (25) Kling, A., and Hutt, P. J.: A.M.A. Arch. Neurol. & Psychiat. *79*:511, 1958. (26) Bond, D. D.; Randt, C. T.; Bidder, T. G., and Rowland, V.: A.M.A. Arch. Neurol. & Psychiat. *78*:143, 1957. (27) French, J. D.: Postgrad. Med. *27*:559, 1960. (28) MacLean, P. D.: A.M.A. Arch. Neurol. & Psychiat. *78*:128, 1957. (29) Schaefer, H.: A.M.A. Arch. Gen. Psychiat. *3*:99, 1960. (30) Cobb, S., in Arieti, S.: American Handbook of Psychiatry, vol. 2, New York, Basic Books, 1959, pp. 1639-1647. (31) Edisen, C. B.: A.M.A. Arch. Neurol. & Psychiat. *79*:323, 1958.

the nature of sleep

Awareness and the state of sleep are two phases of human existence present from birth. Sleep, an intricate phase of living, equals waking in importance. In fact, a phasic variation between the two is necessary to life itself.[1]

Clinically, sleep may be defined as a natural, temporary and periodic state of rest characterized by a diminution of activity and consciousness with a partial loss of response to environmental stimuli.

The causes and nature of sleep have been a source of speculation and fascination since ancient times when Greek philosophers believed that the carotid artery caused drowsiness (*karoo*—I sleep). This belief stemmed from recognition that pressure on this vessel frequently caused unconsciousness.[2]

As a subject of scientific investigation, sleep has been somewhat slighted. Efforts to determine the nature of this phenomenon have been comparatively few and scientific investigation has been limited, even medical men have taken it for granted.[3] Many theories have been hypothesized to explain sleep, but few have been founded on sound scientific fact.

More is known about what happens during wakefulness and periods of sleep deprivation than during actual sleep. In fact, most of the scientific material on this subject deals with wakefulness and concludes that, at least in part, sleep is "...just a condition which occurs in the absence of wakefulness."[4] As recently as seven years ago some physiologists said. "We do not understand either the mechanics of, or the necessity for, sleep."[5]

EARLY THEORIES OF SLEEP

The lack of solid data about sleep has stimulated the proposal of many views, or theories, to explain this phenomenon. Many of these have dealt only with its functional aspects and, with few exceptions, they have all been disproved.[2]

Pavlov, the noted Russian scientist, described sleep as a widespread cortical inhibition.[6,7] Another early investigator described sleep as "...the consequence of a *state of excitation* of certain portions of the central nervous system."[8] Kleitman explains sleep on the basis of the inactivity of the cerebral cortex which results "...from a reduction in the number of afferent impulses, especially from the muscles, reaching the sensorium."[9]

Of the many theories which have been proposed, most have been incomplete or inadequate in their explanation of sleep. The following are of particular interest: the inhibitory theory (proposing that incoming impulses to the cerebral cortex are in some way shut off), which fails to explain why sleep occurs in the newborn infant and the decerebrate animal; the circulatory or cerebral ischemia theory,[2] which also does not account adequately for sleep. It is now known that true cerebral

ischemia, from whatever cause, produces unconsciousness which is not akin to normal sleep. At one time scientists attempted to explain sleep strictly on a humoral or chemical basis.[2]

One of the following was hypothesized: that a substance necessary to wakefulness is replenished during sleep; that a toxic substance or waste product, such as lactic acid, depressed the function of the cortex; or that changes occur in the glands of internal secretion. These theories fall short in several ways: it is now known that "...brain tissue actually derives energy from the oxidation of lactic acid,"[2] and furthermore these theories fail to account for the fact that alertness and efficiency of performance are not at their best immediately on awakening.[10] As knowledge of the physiology of sleep increased, neurophysiologists came to believe that this phenomenon might be based primarily on changes in neural function.[11]

PHYSIOLOGIC CHANGES DURING SLEEP

Sleep usually occurs in a cyclic fashion so that a sleep-wakefulness cycle may be observed. Recurring nocturnal sleep is an acquired habit and is not inborn.[2,10,12] Reduction of sensory stimuli (auditory, visual and proprioceptive—especially of muscle) is particularly conducive to sleep.[10,12]

When they are reduced to, or below, a critical level (as happens by retiring to a comfortable bed in a dark quiet room) "...the sum total of sensory bombardment required to maintain wakefulness falls below a critical level and sleep sets in."[10] The sum total of tonic reflexes of proprioceptive, labyrinthine and visual origin responsible for the upright position in man are most inoperative during sleep. In some species, however, "...postural reflexes are usually not suppressed during sleep; in man they may persist in exceptional conditions...."[12]

During sleep the temperature of the skin is raised,[13] but the body temperature is lowered "...at the beginning and end of a night's sleep."[14] The 24-hour body temperature variation is probably related to the sleep-wakefulness rhythm.[14] Other physiological variables which show a periodicity related to sleep are: basal metabolic rate; pulse rate; heart rate; blood pressure; respiration; sweating; urinary volume; gastrointestinal movements.[2,12-14] "...the pupils [of the eyes] are narrowed, but react to light. The deep reflexes are diminished, and may be lost, ...the cutaneous reflexes are at first increased but later diminished, while the cough reflex...is diminished, but never lost."[13] "The Babinski reflex may be positive."[15]

It has been observed that the depth of sleep fluctuates during the night and, using criteria such as electroencephalographic recordings, depth-of-sleep curves have been plotted.[12] In one night there may be repeated fluctuations in the depth of sleep. "It would seem that the cortex pertaining to the special senses is never fully 'asleep,' the auditory cortex in particular remaining continually on duty...."[13]

Assumption of the reclining, horizontal position, an outstanding characteristic of sleep in man and many animals, permits relaxation of many of the body muscles including the muscles of the jaw, soft palate and uvula. However, complete muscle relaxation does not occur during sleep; special muscle groups may remain contracted except during very deep sleep. The anal sphincter and the

muscles around the eyes and eyelids are contracted. Position is frequently changed during sleep so that different muscles are temporarily brought into play. This may occur as often as 20 to 40 times a night or a total of three to four minutes every night. It involves a semi-awakening which is usually not recalled.[14]

SLEEP REQUIREMENTS

Prior to birth, sleep occurs in an uninterrupted form in the fetus which is exposed to a secure, steady environment without outside stimuli.[16] Following birth, there is a gradual change due to cortical maturation[16] and a marked variation in individual sleep patterns develops; newborn infants still remain asleep most of the time, about 22 out of 24 hours, young children about 12 out of 24 hours, while many adults average 7 to 8 hours of sleep in every 24-hour period.[17]

There is, however, a wide range of sleep and alertness patterns which makes it impractical to set up an average requirement for any age group.[13,14] Generally, an adult may consider that he has had enough sleep if he awakens spontaneously and experiences no feelings of drowsiness or weariness in the middle of the waking period.[10]

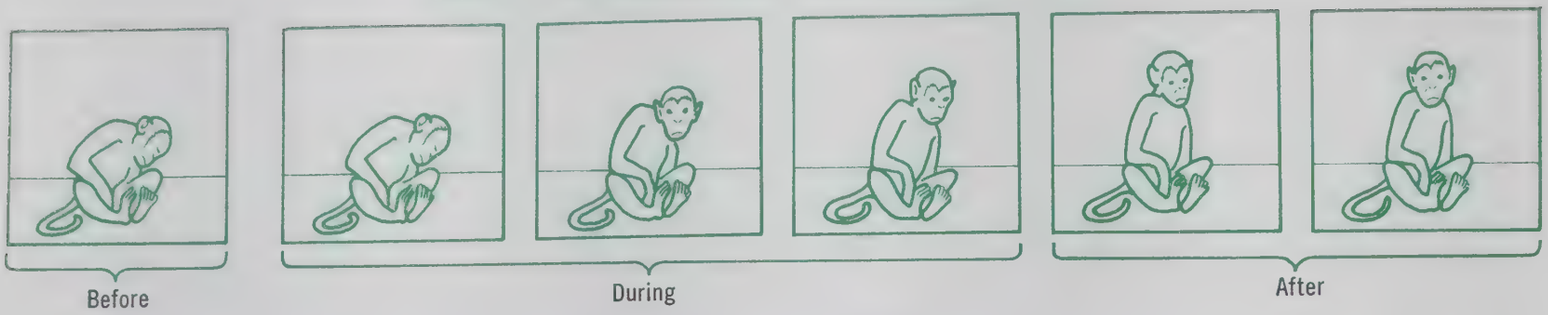
Observations of the sleep behavior of the general population indicate that most people may be classed in one of the following groups:[10] (1) The somatotonic person who tends to be an "early bird"; he rises early, usually performs best at this time but wilts rapidly and retires early. (2) The cerebrotonic person who tends to be at the other end of the scale; dislikes arising at the required hour, is slow to reach maximum functioning level, then stays up late. (3) The viscerotonic person who is both a late riser and an early retirer.

METHODS USED TO STUDY SLEEP

The exact mechanism of sleep remains one of the unanswered questions for those who strive to find out how the brain works. "Sleep is a state in which we spend perhaps a quarter of our lives, and we know practically nothing about the process of going to sleep and awakening."[18] In recent years limited knowledge has been obtained by observation and experimentation. Progress in this field was slow until the contrasting states of sleep and wakefulness were found to be associated with changes in the electrical activity of the cerebral cortex. The discovery of electroencephalography by Berger[19] led to his observation that characteristic patterns tend to be different during sleep and wakefulness.

The pioneer observations of Rheinberger and Jasper[20] (1937) laid the basis for contemporary investigation. Using the cat, they undertook the first combined electroencephalographic and behavioral study of the evocation of wakefulness by afferent stimulation. "...the importance of afferent stimulation in initiating EEG [electroencephalographic] and behavioral wakefulness suggested the important role also of a central mechanism with a more general influence and a greater intrinsic capacity for maintained excitation than the specific afferent pathway."[20]

DIAGRAM OF MONKEYS SHOWING BEHAVIORAL AROUSAL
EVOKED BY PERIPHERAL AFFERENT, OR RETICULAR STIMULATION



Adapted from Segundo, J. P.; Arana-Iniquez, R., and French, J. D.: J. Neurosurg. **12**:601, 1955.

Another historic contribution was made by Bremer[21] (1937), who first observed that "...the electrical activity of the cerebral hemispheres... [of a decerebrate animal] was one of a waking pattern following a bulbo-spinal section while, after a section through the midbrain, the record was that of sleep." Bremer concluded that deafferentation of the cerebrum leads to sleep.[21] Wakefulness could then conversely be attributed to maintained corticipetal conduction of afferent impulses.

Studies of neoplastic or encephalitic lesions found in the brain stem of patients with lethargy, somnolence or abnormal sleep as outstanding symptoms have shown that diencephalic and mesencephalic centers play important roles in sleep and wakefulness.[12] Periodic electroencephalographic and microencephalographic records have also revealed much about levels of consciousness, depths of sleep, and dreaming.[22-27]

A recent report on an investigation of the effect of several types of perceptual stimuli during sleep has shown that subliminal stimuli are utilized in the formation of dreams.[28]

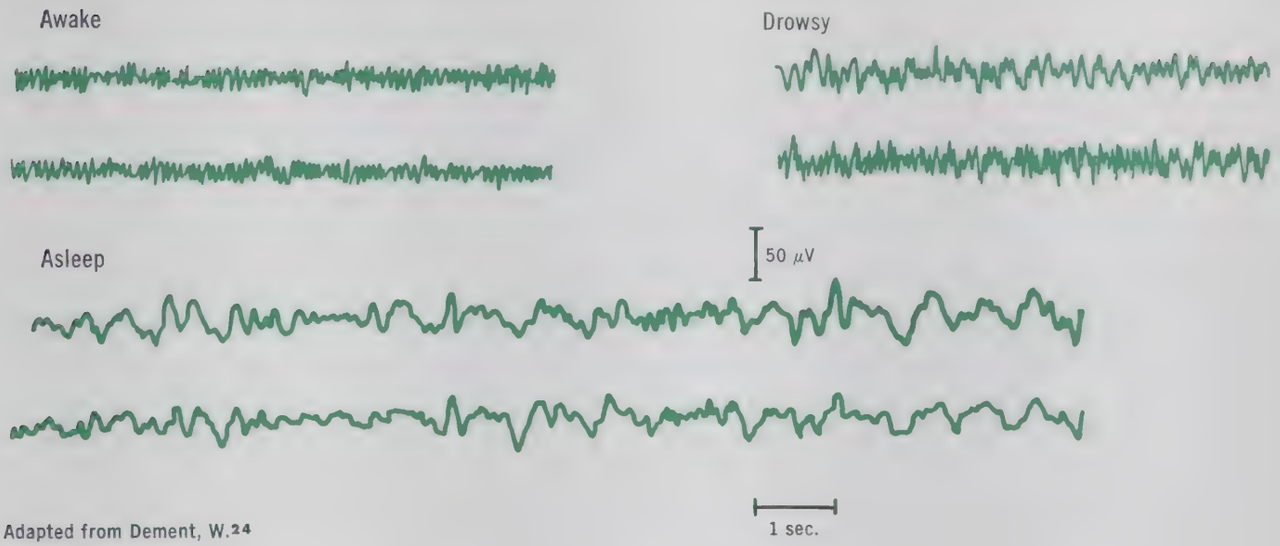
Much has also been learned from close observation and study of animals and human subjects kept awake forcefully for prolonged periods of time. While dogs may die after 14 days, the period of wakefulness that would be lethal to human subjects is not yet known.[2]

Kleitman[9] studied human subjects kept awake forcefully for 60 to 114 hours and, more recently, Tyler[29] studied some 600 patients who went without sleep for as long as 112 hours. These investigators noted minimal changes in body chemistry and physiological functions during these periods. Kleitman found minimal changes in, or impairment of, mental processes during periods of forced wakefulness. However, Tyler found that notable psychological changes occurred after 30 to 60 hours; these included: memory loss, irritability, inattention and illusions or hallucinations. These alterations in behavior varied from mild to severe; some resembled an acute schizophrenic reaction.

It appears that lack of sleep can destroy cortical functions and, in animals, changes in the nerve cells of the cortex, including chromatolysis and shrinkage of cell bodies, can be demonstrated after prolonged periods of forced wakefulness.

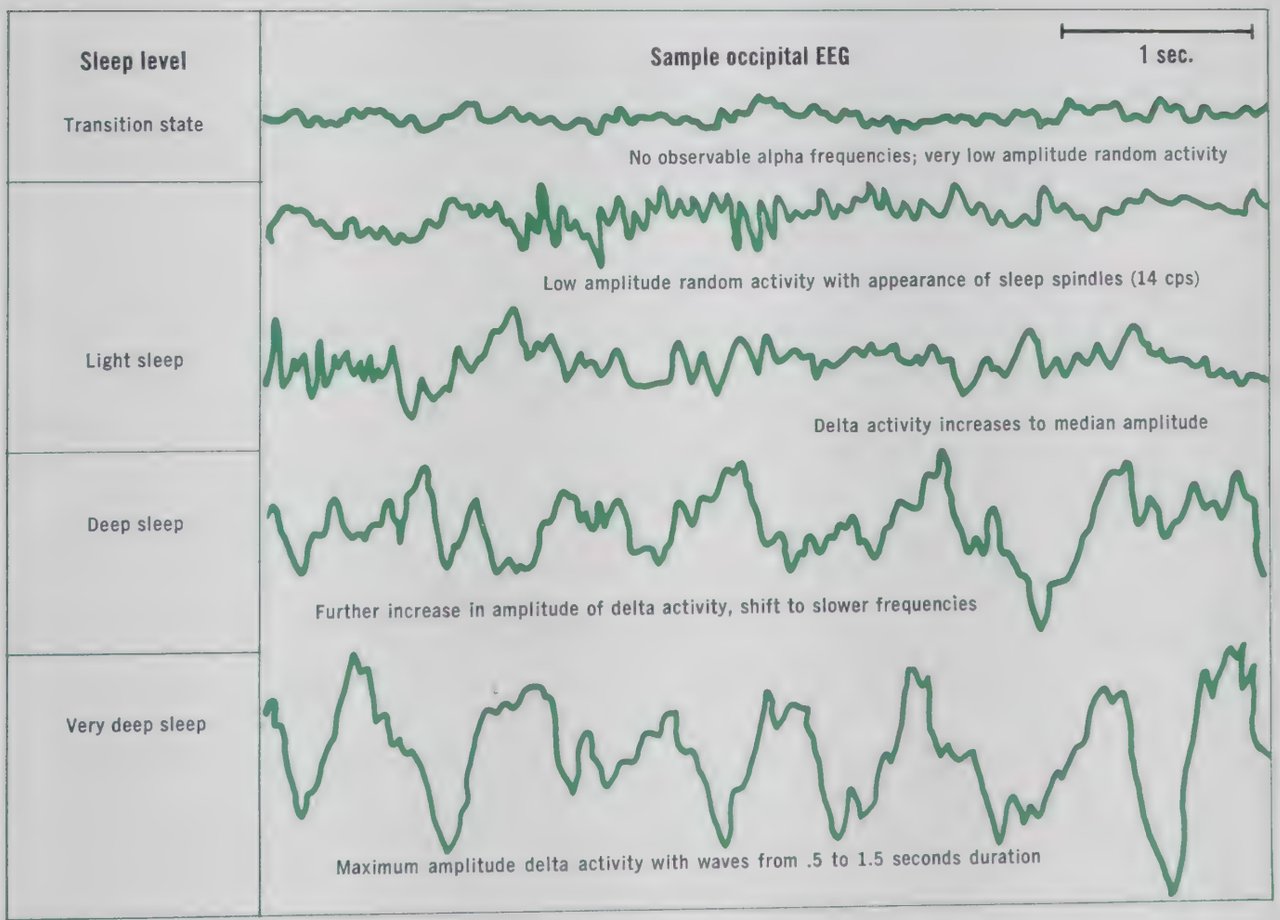
Study of the sleeping individual also indicates marked involvement of specific nervous centers. This is evidenced by characteristic and different electroencephalographic tracings for sleep and wakefulness,[22,23] as well as by reflex changes.[5,15]

ELECTROENCEPHALOGRAPHIC TRACINGS IN CATS DURING SLEEP AND WAKEFULNESS



Adapted from Dement, W.[24]

ELECTROENCEPHALOGRAPHIC TRACINGS IN MAN DURING SLEEP



Relation of varying depths of sleep and wakefulness as demonstrated by changes of the amplitude and frequencies of delta-type waves in electroencephalographic recordings.

Adapted from Simon, C. W., and Emmons, W. H.[22]

THE SLEEP MECHANISM—NEUROANATOMICAL CONSIDERATIONS[25,26,30-34]

Anatomically the following play a major role in sleep and wakefulness: (1) the classic afferent pathways (especially proprioceptive); (2) the reticular formation in the brain stem; (3) the cerebral cortex; and (4) the ascending and descending connections between the cerebral cortex and the reticular formation.

Experiments have indicated that all afferent impulses to the brain contribute to two great ascending systems. These are the long, direct, compact lemniscal pathways which are the classic neurophysiologic projections that go to discrete cortical receptive areas. In addition, there are extralemniscal pathways.[25] The reticular formation (RAS) receives all afferent sensory tracts, or collaterals from them.[25,26,30-32] Anatomic and physiologic evidence indicates that the (RAS) sends fibers to various parts of the CNS[26,30] including the cerebral cortex, the cerebellum, the hypothalamus and internuncial pools[33] at various levels. This is contrary to earlier thought—that afferent pathways go directly to the cerebral cortex without such connections.

One ascending lemniscal pathway projects widely from the cephalic end of the reticular formation to the cerebral cortex probably influencing discrete cortical receptive areas.[26] Extralemniscal pathways project from the central and caudal reticular formation and probably influence the cortex diffusely.[25]

There is evidence that certain areas of the cortex project (usually directly) into the reticular formation, while others do not.[25] These downward projections are called corticofugal pathways. Areas which are known to have such projections are: frontal eye field region; sensorimotor cortex; paraoccipital region; orbital surface of the frontal lobe; first temporal gyrus; and medial cingulate gyrus.[27]

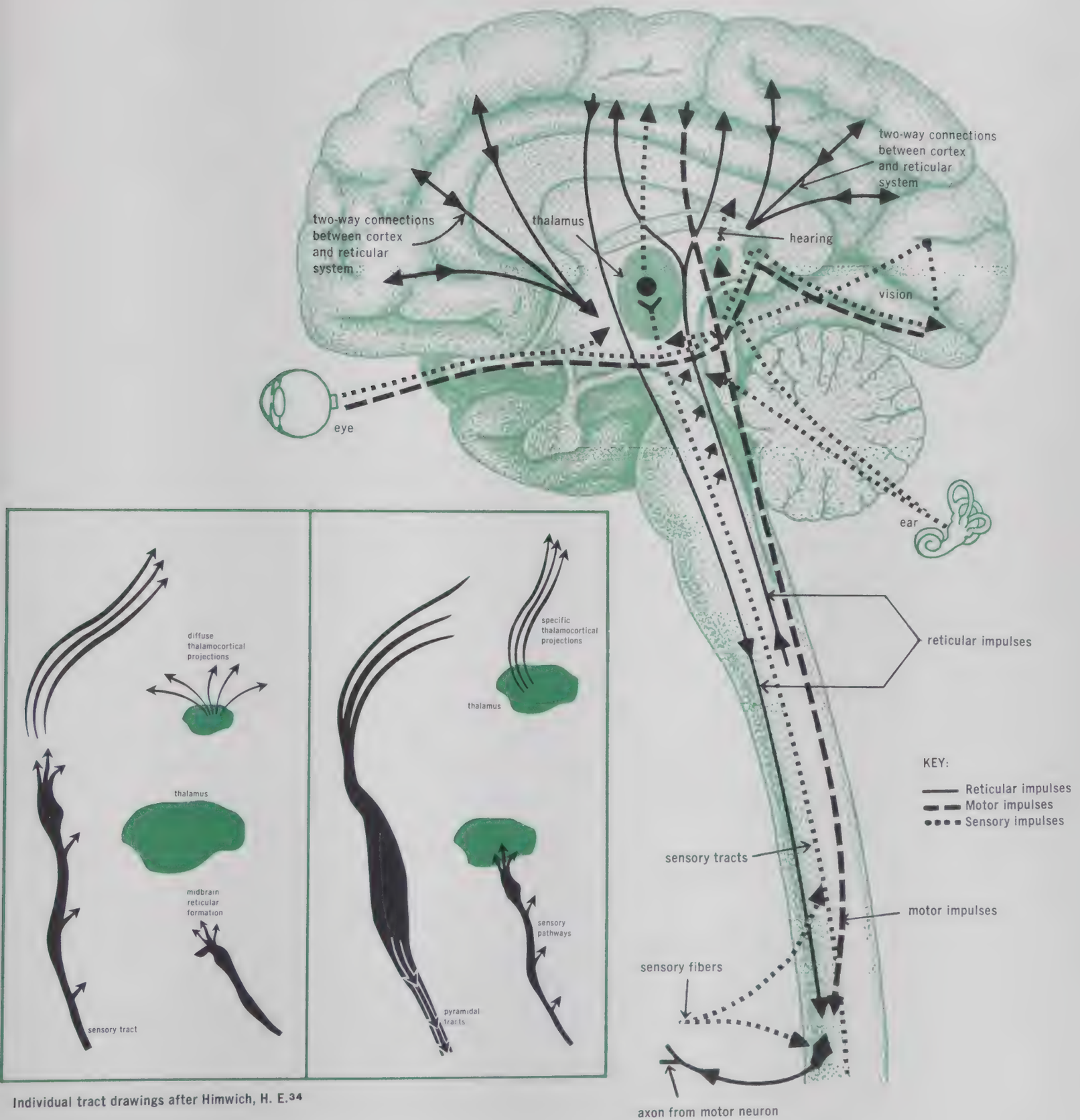
PRESENT CONCEPT OF SLEEP

A conclusive and comprehensive explanation of the sleep mechanisms would currently be impossible as much remains hypothetical or unsolved. Sleep mechanisms are probably much more complicated than is now known. The following material is presented with this in mind.

It is presently thought that cortical as well as subcortical or brain-stem mechanisms contribute to sleep and arousal.[35,36] The current concept is that there is a subcortical "alerting" or "arousing" center, the reticular formation (reticular activating system—RAS) located in the midbrain, which stimulates activity and promotes wakefulness and alertness.[4,30-32,36]

The RAS is thought to activate both cortical and subcortical structures.[37] Experimentally, subtotal injury to the RAS results in a stuporous condition.[25] Lesions of the posterior part of the hypothalamus have also been shown to produce somnolence and deep sleep.[4] "This sleep has many characteristics of normal sleep...." and is partly reversible if the stimulus is sufficiently strong.[4] It has been shown that some subjects in stupor may be aroused for brief periods.[25] This suggests that the RAS alone does not control sleep and wakefulness.

ANATOMIC AREAS AND PATHWAYS CONCERNED WITH SLEEP



Individual tract drawings after Himwich, H. E.[34]

Although man and decorticate animals exhibit brief periods of arousal, they do not react appropriately to environmental stimuli.[38] Apparently "...crude arousal is possible without cortical contribution..." but the cortex must be intact "...for prolonged, sustained alert wakefulness characteristic of the normal adult subject."[38]

The classic afferent pathways indirectly promote cortical activity and produce wakefulness. They exert their influence at subcortical levels by sending collaterals to the ascending RAS. Sensory stimuli have been found to serve a twofold function; (1) by making environmental information available, they provide specific data concerning reality, and (2) they arouse, or alert, the organism and make it more aware of stimuli in general.[39] In sleep, of course, there is a reduction of sensory stimuli. Fewer sensory impulses mean fewer impulses to the RAS to arouse and alert the organism. When the afferent impulses are insufficient for wakefulness, the RAS, which has a generalized influence upon the cortex, may discharge to the higher center and thus maintain the wakeful state.[39] "Neuron thresholds can be lowered by impulses from other neurons, and the nonspecific activating system from the reticular formation, particularly, has just such an effect upon cortical neurons."[40]

The RAS is responsive to stimuli applied to all sensory systems and its cells are probably capable of firing spontaneously. This is probably not always sufficient to prevent sleep.[26] It is known, however, that the RAS is able to maintain wakefulness at levels of visceral and somatic stimulation. There is experimental evidence that the RAS functions in both an ascending and descending fashion.[38,39] It exerts influence on lower motor outflows and upon higher centers, and can thereby influence both central awareness and behavior.

Depth of sleep is a function of the state, or reactivity, of the ascending RAS. At the end of a night's sleep its sensitivity rises and environmental stimuli are increasingly capable of promoting cortical arousal.[13] At this time complete arousal is more apt to occur.

Animal experiments indicate that under certain circumstances the cerebral cortex is capable of activating itself. This indicates that, in addition to the action of the RAS on the cerebral cortex, a reverse phenomenon exists placing the RAS under control of cerebral cortical influences as well as peripheral sensory stimuli.[14] It is known that thought can either stimulate the RAS or, inversely, encourage it to rest or remain indifferent.

selectivity of stimuli—Different sensory stimuli vary in their abilities to stimulate the organism. The meaning of the stimulus to the individual is important. For example, a sleeping mother may be unbothered by thunder, street noises, trains, etc., but rapidly awakened by the first faint whimper of her infant.[13,39] The cortex, it seems, is capable of controlling sensory stimuli which are relayed to it. This control, of course, is modified by the RAS through which the impulses are relayed.[33,37]

synchronization of neurons in sleep—Recent studies,[41] by means of microelectrodes, have shown a previously unnoted change in the electrical activity of the brain in the transition from wakefulness to sleep (natural or induced). This has been "...described as a passage from a 'desynchronized' to a 'synchronized' state."[41] This "...synchronization is accompanied by a grouping, and desynchronization by a lack of grouping of...[the] action-potentials" of cortical and thalamic neurons. "On the basis of the time, phase, and amplitude characteristics..." it is thought that "...some of the neurons of the diffuse thalamic projection system (RAS) become active in a regular sequence...."[41] Presently the significance of this finding is not known.

PSYCHOLOGICAL SIGNIFICANCE OF SLEEP AND DREAMING

Human sleep deprivation experiments[2,14] have demonstrated that sleep is more important to the nervous centers and brain than to the rest of the body. It is indicated that sleep fills a basic role in man's psychologic life and is a vital human process. It serves as a stabilizing mechanism which permits, and is necessary for, a reorganization and selective discarding of problems.

Sullivan[1] points out that the division of life between sleep and wakefulness varies inversely with developmental age and that there are several levels of sleep. Anxiety may affect the level of sleep or the ability to fall asleep, and the more that sleep is needed the greater may the disruptive anxiety or tension state become.

In sleep many things are done which cannot be done in the waking state because security mechanisms and the individual's "self" are relatively dormant. Thus, "...quite often much more meaningful behavior occurs in states of light sleep than at any other time...."[42] Sleep is an important phase of living and a part of life in which the individual is relieved of the necessity of maintaining security and in which needs, unsatisfied during wakefulness, are taken care of, or "...satisfied by symbolic operations in such a way that they don't make trouble."[42] In this way the individual is kept "psychologically comfortable."

Sullivan also points out that in our social order many needs have to be thwarted or postponed. These urgencies may be successfully discharged in sleep and it is by these "extraordinarily complex, more or less continuous operations" which he calls "dynamisms of difficulty" that the individual can maintain a semblance of comparative mental health. These "dynamisms" are part of the equipment of the well-adjusted person but may also be seen as explanations of serious trouble.[42] Dreams "...represent a relatively valid parataxic operation for the relief of insoluble problems of living,"[1] and recent experiments on the effect of dream deprivation suggest that "...a certain amount of dreaming each night is a necessity."[43]

Sleep studies show "...that most of the dream experience in normal sleep is never recalled."[23] Therefore, dreams are seldom adequate for use in psychiatry unless the dream has been brief and marked by great emotion.[1] The psychiatrist in his study of personality does, however, work with recalled survivals from dream life as diagnostic and therapeutic aids,[42,44] since in the dream world he sees evidence of the tensions which are being sublimated in the waking state.[42]

EFFECT OF SEDATIVES AND TRANQUILIZERS ON CONSCIOUSNESS

Recent experimental studies, using animals and humans, have helped to clarify the mode and site of action of various drugs acting on the central nervous system. Himwich[34] found that phenothiazines and barbiturates depress the RAS, diminish alertness and intensify electroencephalographic sleep patterns. However, his studies also showed that rauwolfia stimulated the RAS and increased alertness. Phenothiazines and rauwolfia alkaloids acted alike in that they apparently blocked the Papez circuit (which is thought to correlate the emotional and intellectual aspect of consciousness), although the latter were found somewhat less sedative in their action.[34]

Clinically the tranquilizers and the barbiturates differ in their effects on consciousness. Experimentally this is marked by a significant contrast in their action on the neocortex,[34] the center for discriminative aspects of consciousness such as seeing, hearing and speech, and upon the respiratory centers. Meprobamate, as well as the phenothiazines and rauwolfia derivatives, has no effect on the neocortex.[34]

General anesthetics depress the RAS but, unless large doses are given, leave respiratory and vasomotor reticular neurons relatively intact. "The neuroanatomic complexity of these structures makes the analysis of site of drug action in the reticular formation extremely difficult."[45]

SITE AND EFFECT OF DRUG ACTION ON CNS

SITE	FUNCTION	PHENOTHIAZINES	RAUWOLFIA DERIVATIVES	MEPROBAMATE	BARBITURATES
THALAMUS	Transmission of alerting impulses to cortex. Modulation of action of reticular formation (Recruitment)	+	0	—	+
RETICULAR FORMATION	Alerting: Behavior and/or EEG. Associated with function of Papez circuit	—	+	0	—
LIMBIC SYSTEM (Papez Circuit) Hippocampal and/or amygdaloid seizures	Correlates emotional and intellectual aspects of consciousness	+	+	—	—
NEOCORTEX	A source of discriminative aspects of consciousness	0	0	0	—
HYPOTHALAMUS	Regulation of autonomic functions, correlating them with motor activities	Sympathetic: —	Sympathetic: — Parasympathetic: +	0	—
RESPIRATORY NUCLEI	Initiation and regulation of respiration	0	0	0	—
NEUROHORMONAL DEPOTS	Regulation of affective behavior	Block neurohormones	Deplete neurohormonal stores	0	0

Adapted from Himwich, H. E.[34]

+: stimulation —: depression 0: no effect

SLEEP THERAPY IN PSYCHIATRY

Sleep therapy has been used as a method of controlling "mental derangements" since ancient times. This form of therapy presently holds a prominent position in Europe, especially in the U.S.S.R.[46]

The effectiveness of prolonged sleep is theoretical but appears to offer some promising possibilities both as a primary and adjuvant tool in psychiatry. One group of 25 patients who had not responded to other forms of therapy treated in this way included 8 schizophrenics, 2 manic-depressives, 3 obsessive-compulsives, 9 mixed psychoneurotics, 2 cases of hysteria and 1 case with character neurosis. There was a 60 per cent improvement rate in this group of patients.[46] On the basis of this study the following are a tentative list of indications: neuroses, particularly conversion hysteria, anxiety hysteria, and borderline cases with predominance of hysterical and anxiety symptoms; manic-depressive psychoses; schizophrenic reactions with preponderance of affective alterations and excitation. Obsessive-compulsive patients appear to benefit very little from sleep therapy.[46]

Bibliography: (1) Sullivan, H. S.: The Interpersonal Theory of Psychiatry, New York, Norton, 1953. (2) Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 6, Baltimore, Williams & Wilkins, 1955, pp. 1066-1071. (3) Critchley, M., in Burns, C.: New Zealand M. J. *58*:584, 1959. (4) Ingram, W. R., in Field, J.: Handbook of Physiology, Sect. 1: Neurophysiology, vol. 2, Washington, D. C., American Physiological Society, 1960, pp. 951-978. (5) Main, R. J., and Richardson, A. W.: Physiology, ed. 2, St. Louis, Mosby, 1953, pp. 151, 152. (6) Pavlov, I. P.: Lectures on Conditioned Reflexes and Psychiatry, New York, International Publishers, 1941, p. 89. (7) Pavlov, I. P.: Lectures on Conditioned Reflexes, New York, International Publishers, 1928, pp. 305-308. (8) Hess, W. R.: Am. J. Physiol. *90*:386, 1929. (9) Kleitman, N., cited in Best, C. H., and Taylor, N. B.: *op. cit.* (ref. 2). (10) Kleitman, N.: Am. J. Nursing *60*:677, 1960. (11) Brain, W. R.: Diseases of the Nervous System, ed. 3, New York, Oxford, 1947, pp. 858, 859. (12) Houssay, B. A., *et al.*: Human Physiology, ed. 2, New York, McGraw-Hill, 1955, pp. 1113-1116. (13) Burns, C.: New Zealand M. J. *58*:584, 1959. (14) Kleitman, N., in The Cyclopedia of Medicine, Surgery, Specialties, vol. 12, Philadelphia, Davis, 1954, pp. 733-740. (15) Grinker, R. R., and Bucy, P. C.: Neurology, ed. 4, Springfield, Ill., Thomas, 1949, p. 187. (16) Cruden, W. V.: Brit. J. Clin. Pract. *14*:475, 1960. (17) Grant, I. D.: New Zealand M. J. *58*:431, 1959. (18) Cobb, S., in Arieti, S.: American Handbook of Psychiatry, vol. 2, New York, Basic Books, 1959, p. 1646. (19) Berger, H., cited in Magoun, H. W.: The Waking Brain, Springfield, Ill., Thomas, 1958, p. 64. (20) Rheinberger, M., and Jasper, H. H., in Magoun, H. W.: *ibid.*, pp. 64-66. (21) Bremer, F., in Magoun, H. W.: *ibid.*, p. 66. (22) Simon, C. W., and Emmons, W. H.: Science *124*:1066, 1956. (23) Dement, W., and Kleitman, N.: EEG Clin. Neurophysiol. *9*:673, 1957. (24) Dement, W.: EEG Clin. Neurophysiol. *10*:291, 1958. (25) Magoun, H. W.: Clin. Neurosurg. *3*:186, 1955. (26) French, J. D.: J. Neurosurg. *15*:97, 1958. (27) French, J. D., *et al.*, cited in Livingston, R. B.: Clin. Neurosurg. *3*:192, 1955. (28) Fisher, C.: Am. J. Psychiat. *116*:1009, 1960. (29) Tyler, D. B., cited in Best, C. H., and Taylor, N. B.: *op. cit.* (ref. 2). (30) Harris, G. W., in Jasper, H. H., *et al.*: Reticular Formation of the Brain, Boston, Little, 1958, pp. 207-209. (31) Natua, W. J. H., and Kuypers, H. G. J. M., in Jasper, H. H., *et al.*: *ibid.*, pp. 3, 4. (32) Livingston, R. B., in Jasper, H. H., *et al.*: *ibid.*, p. 178. (33) Livingston, W. K.; Haugen, F. P., and Brookhart, J. M.: Neurology *4*:485, 1954. (34) Himwich, H. E.: Tranquilizers, Barbiturates and the Brain, Scientific Exhibit, 109th Ann. Meet., A.M.A., Miami Beach, Florida, June 13-17, 1960. (35) St. Onge, K. R., and Calvert, J. J.: J. Speech & Hearing Disorders *24*:43, 1959. (36) Magoun, H. W.: The Waking Brain, Springfield, Ill., Thomas, 1960, pp. 64-77. (37) Livingston, R. B.: Clin. Neurosurg. *3*:192, 1955. (38) French, J. D., in Field, J.: Handbook of Physiology, Sect. 1: Neurophysiology, vol. 2, Washington, D. C., American Physiological Society, 1960, pp. 1281-1305. (39) Linn, L.: Am. J. Psychiat. *110*:61, 1953. (40) Gerard, R. W., in Arieti, S.: American Handbook of Psychiatry, vol. 2, New York, Basic Books, 1959, p. 1634. (41) Verzeano, M.: Science *124*:366, 1956. (42) Sullivan, H. S.: Clinical Studies in Psychiatry, New York, Norton, 1956. (43) Dement, W.: Science *131*:1705, 1960. (44) Weiss, E., and English, O. S.: Psychosomatic Medicine, ed. 3, Philadelphia, Saunders, 1957. (45) Domino, E. F., in Jasper, H. H., *et al.*: Reticular Formation of the Brain, Boston, Little, 1958, pp. 296, 297. (46) Azima, H.: J. Ment. Sc. *101*:593, 1955.

the blood-brain barriers

A CONCEPT AND DEFINITION

THE NEED FOR A CONCEPT

The concept of a "Blood-Brain Barrier," notwithstanding more than 50 years of experimental attempts to establish its validation as a physiologic principle, remains "conceptual." Its mechanism, its composition and site, are still obscure[1,2] but its physiologic role takes on greater significance in the light of the ever-increasing prominence of psychopharmacology. Although there may be three anatomically different metabolic exchange areas for the central nervous system, generally these are functionally similar; hence the use of the plural term "barriers" as the overall title of this discussion. Some distinctions have been made between the blood-brain, blood-cerebrospinal fluid and cerebrospinal fluid-brain exchange barriers. However, for purposes of this presentation, the term blood-brain barrier will be employed generally for exchanges between blood and central nervous system. When one specific functional area only is implicated, this is indicated in the text.

BACKGROUND HISTORY

This idea of a "barrier" is not unique to the brain, for it is now well recognized, for instance, that certain antibodies may, in some species, pass the barrier of the placenta between the maternal and fetal blood.[3] According to Driscoll and Hsia,[4] in 1885 Ehrlich suggested the existence of a barrier between content of the blood vessels in the brain and the brain matter when he observed that, with the exception of the brain, all body viscera rapidly became discolored following the intravenous injection of acid aniline dyes. Evidence obtained from these[4] and other studies[5] based on dyes has been challenged on grounds that they are foreign to the body. Over 50 years ago, "...it was first noticed that the central nervous system differs from other organs as far as the uptake of substances from the blood stream is concerned."[6] More recently, the introduction of isotopic techniques has afforded improved means of studying this rate of exchange of physiologic solutes and solvents between blood and brain.[7] New data has made available substantial information on this dynamic equilibrium.[6]

THE PRINCIPLE AND IMPLICATIONS

There still is difference of opinion as to the site of the BBB (blood-brain barrier).[8] Whatever its specific locus, however, "...the blood-brain barrier appears to express the selective permeability of living tissues."[5] Presenting the basic principle, Bakay[2] states "...that practically all particulate matter circulating in the blood is either prevented from entering the central nervous system, or delayed in so doing by a physiological mechanism which is not known as yet in every detail." Although some have regarded the term "blood-brain barrier" as misleading or obsolete, until more knowledge is obtained, any other term would suggest specific physiologic or anatomic explanations and would be only hypothetic.[2]

That the blood-brain barrier is not only theoretic but of significant practical import may be perceived as its experimental implications and clinical applications are elucidated.

PROBLEMS IN EXPERIMENTAL STUDY

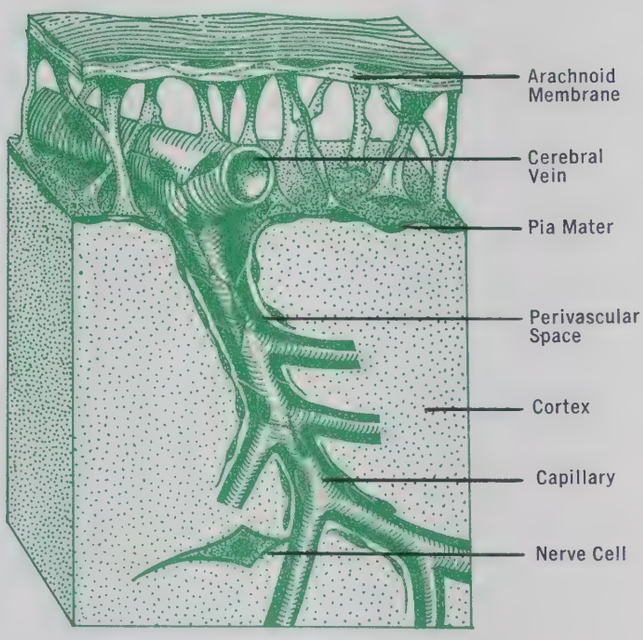
Some of the difficulties encountered in establishing this concept as a solidly acceptable theory are those of experimental technique. Artifacts resulting from technical procedure, in this field particularly, may present misconceptions of form and function. Also, one cannot visualize blood-brain exchanges apart from dynamic aspects. Thus, for example, as a result of differences in regional vascular density, there might be explainable variations in the penetration of any one substance into the nervous system—without recourse to the concept of a BBB.[8]

STRUCTURE OF THE BLOOD-BRAIN BARRIER

ANATOMY AND HISTOLOGY

From what has been stated above, and based on our still too meager knowledge, a definite anatomic and histologic structure cannot yet be ascribed to the "barrier." Structural characteristics of capillaries in brain parenchyma are illustrated in fig. 1. Although there is considerable difference of opinion, many investigators perceive the BBB as the capillary wall.[2] Another suggested locus is the perivascular glial mantle.[5] It has been suggested that the glial substance may be mobile, rather than fixed, and that it is separated from the vessel by an ill-defined ground substance.[8]

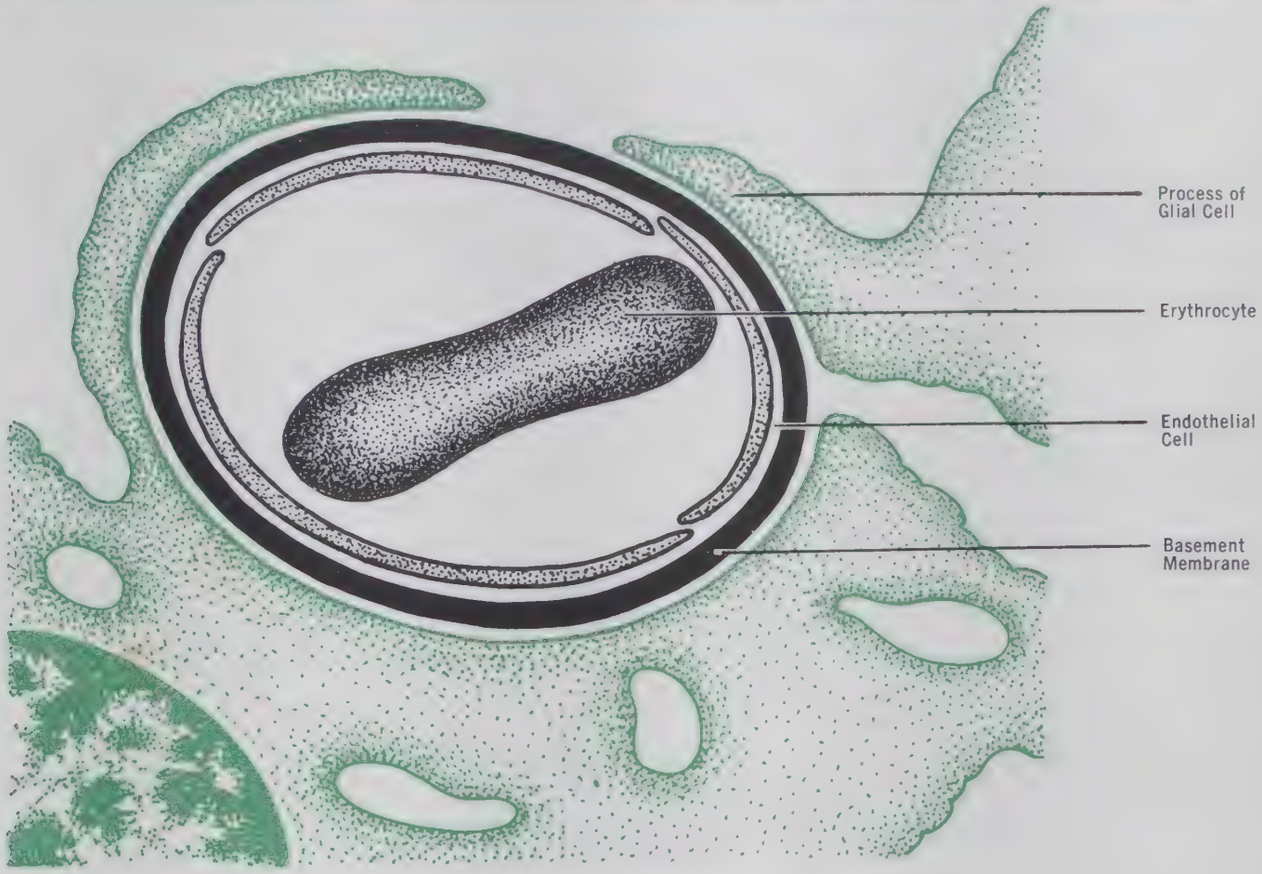
Fig. 1 Diagrammatic Representation of Capillary in Brain Parenchyma



Adapted from Ranson, S. W., and Clark, S. L.[9]

In great part, the cerebral capillaries are in close relationship to the neuroglial processes which invest almost entirely the capillary basement membrane. Ranson and Clark[9] consider these as forming the model of the conceptual BBB, and it may be that these special features are responsible for the "chemical design"[10] of the c.s.f. (cerebrospinal fluid) and "...related to the special physiologic relations between the blood stream and the cerebrospinal and interstitial fluids of the nervous system...."[10] It is this area (shown in fig. 2) which presents the chief target for investigation.

Fig. 2 Representation of Capillary Area Illustrating Structural Conception of the BBB (based on an electron photomicrograph)



Adapted from Maynard, E. A.; Schultz, R. L., and Pease, D. C., in Livingston, R. B.[10]

DEVELOPMENT OF THE BARRIER

Certain phenomena indicate that the BBB is not fully developed at birth.[11] For instance, metabolic studies indicate that with advancing age the brain undergoes a changing permeability to intravascular substances.[4] Bakay,[11] studying the embryonic development of the BBB by injecting radioactive P^{32} into rabbits of various ages, found a more rapid turnover of the isotope in fetal and neonatal brains than in the adult animal.[11] The amount of uptake of certain substances by the brain is apparently, then, a reflection of maturation level. The greater permeability has been attributed by some to incompletely developed enzyme systems.[4] The experimental observation of the greater permeability in the immature brain has particular clinical application as will be seen in the discussion of kernicterus.

BARRIER OR BARRIERS?

It should be recognized "...that certain areas of the brain have a reduced or absent blood-brain barrier (for example, the area postrema, paraphysis, supraoptic crest, tuber cinereum and wall of the optic recess)."[12]

In addition, not being a fixed histologic entity, the structure of the conceptual BBB presents rather a wide variation—from endothelium alone to the capillary endothelium and columnar epithelium of the choroid plexus.[9]

Since "blood-brain barrier" implies passage only from blood to parenchyma, distinctions have been made between blood-brain, blood-cerebrospinal fluid (c.s.f.) and c.s.f.-brain barriers. Thus, it has been shown that transfer of most substances from c.s.f. to brain is more rapid than transfer of such substances from the blood to the brain.[6] Since the effect of each barrier on solute transfer and homeostatic function is generally similar, for discussion purposes, these may be considered together.[7]

THE NATURE OF THE BARRIER

EXPERIMENTAL STUDY

Because of the diversity of experimental techniques employed, correlating data toward final solution of the BBB—wherein it resides and whether or not it is a phenomenon of capillary permeability—has been difficult.[2] Data of quantitative value is now obtainable for the first time by the use of radioactive tracers[2,13] which make possible observation of changes under normal and pathologic conditions without detriment to the patient.

Among factors which appear to affect the BBB, clinically or experimentally, are age,[14] body size, anoxemia,[15] electroshock,[16] certain chemical agents,[2,7,17] and body temperature.[18] Some of the experimental variations have been noted to be of clinical significance.

PHYSIOLOGIC EVIDENCE

The barrier exhibits delayed permeability to practically all solutes (such as urea and glucose) which readily pass into other tissues and, unlike other cell or capillary membranes, it is extremely impermeable to proteins, including bacterial toxins and antibodies.[7] Although they readily penetrate membranes elsewhere, penicillin, bile pigments and many other substances do not cross the normal blood-brain barrier.[10] The selectivity of the BBB is well illustrated by the fact that glutamine apparently crosses the BBB readily whereas glutamic acid is apparently blocked.[4]

THEORETIC MECHANISMS OF ACTION

Many physiologic mechanisms have been proposed to explain functions of the cerebral barrier. As already indicated, the theories implicating the capillary membrane,[1] intercellular cement,[19] or pia-glia, described by Bakay,[2] are all open to criticism. Theories oriented toward a consideration of the lipoid solubility or of the electric charge of the test substance have also been presented.[2,6] More recently, barrier function has been attributed to several enzyme systems.[6] In part, this has been suggested by the effect of enzyme inhibitors. Thus, when cholinesterase or carbonic anhydrase are

inhibited, an increased penetrability of the BBB may cause elevation of barbiturate concentration in the brain. Many investigators[20] have suggested "...that the monoamine oxidase may play a role in the so-called blood-brain function."

FUNCTIONAL SIGNIFICANCE

Certain inferences have been drawn as to the permeability of the BBB: (1) Passage of potassium, phosphorus, chloride and sodium is delayed; (2) Penetration of the brain by bromide, nitrate, sulfate and thiocyanate ions is severely limited; (3) Aniline dyes, certain viruses, toxins and drugs are excluded.[5]

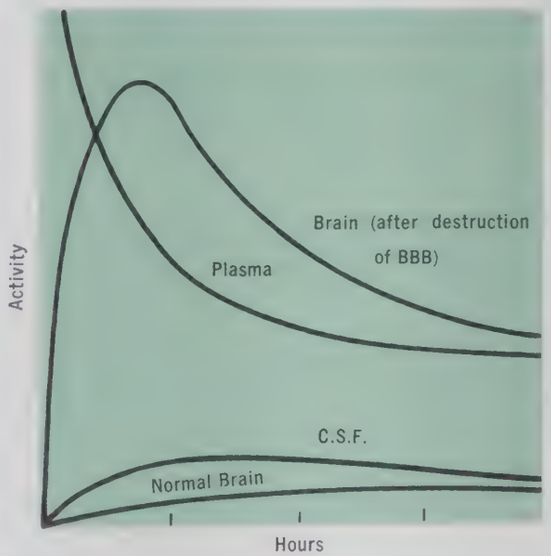
The feelings of many investigators are perhaps reflected in the observation by Gerard: "It is not impossible that the major function of the blood brain barrier and of the glia is to stabilize the composition of the intercellular fluid of the nervous system and so the internal environment in which the neurones function, at least there is accumulating highly suggestive evidence of such a role."[21]

APPLICATION OF THE CONCEPT

What passes and what may not pass the BBB has profound implications—for the ions, chemicals and fluids bathing the brain contribute to its functions. Although having its most direct application in psychopharmacology, the concept of the BBB has figured significantly in other research. It has been assumed, for instance, that the diffuse lesions of brain parenchyma in allergic encephalomyelitis represent sites "...of increased permeability of the barrier system."[22]

As a specific example, physicians, especially neuropathologists, are "...concerned with the transport of viruses and large molecules to the brain and their dissemination in the cerebral tissue."[1] It should be noted also that certain pathologic processes[23] may decrease as well as increase barrier permeability. Some applications of the barrier concept will be discussed briefly.

Fig. 3 Exchange of P^{32} Between Plasma and Brain After Destruction of Blood-Brain Barrier



Adapted from Bakay, L., in Richter, D.[6]

INFECTION AND TRAUMA

The differences in penetrability of the BBB by various antibiotics are generally well known.[7] Bacterial infections themselves frequently alter the barrier[6]—in tuberculous meningitis the level of streptomycin in the c.s.f. may correlate with the state of the disease.[7] Various types of brain trauma apparently increase the barrier permeability (fig. 3) making possible the en-

trance of a neurotropic virus.[22] Studies with dyes indicate that following a wound, consequent barrier disruption may be restored in about 10 days.[22]

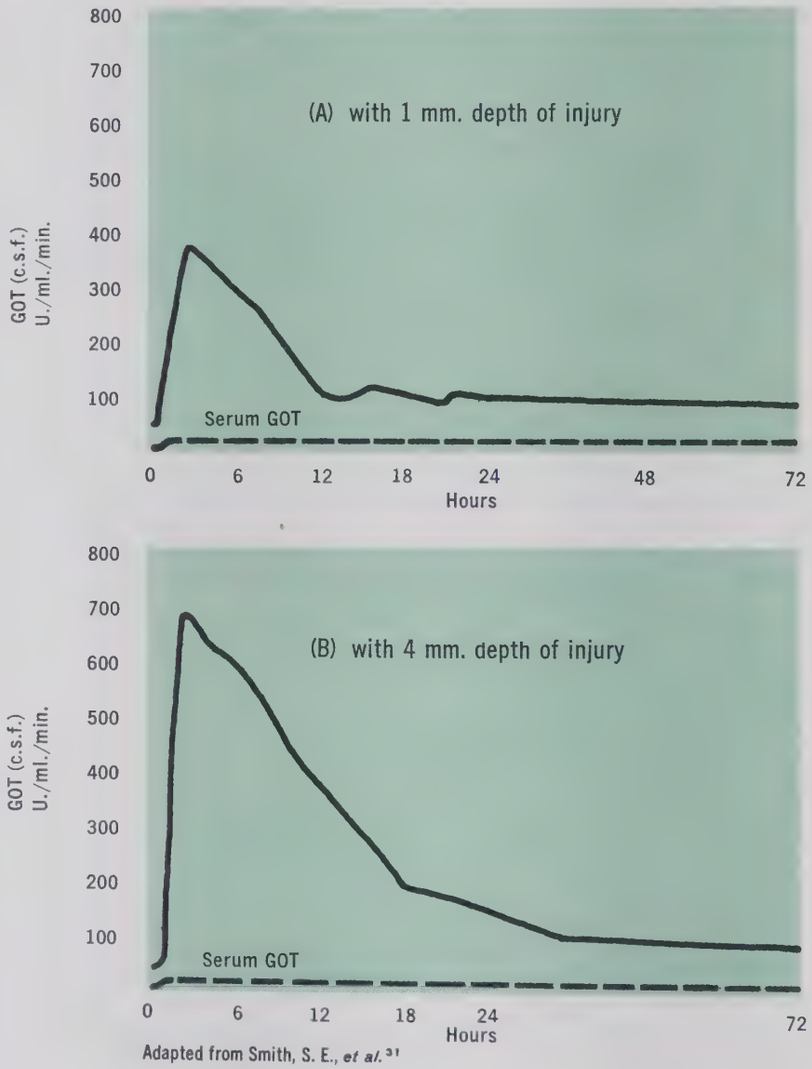
KERNICTERUS

As a cause of mental retardation, the clinical condition known as kernicterus, or bilirubin encephalopathy, accounts for only 3 per cent of cases.[24] Although the development and dynamics are little understood, this pathologic staining in the neonatal period has been attributed in part to the greater permeability of an immature BBB, as well as the elevated bilirubin levels.[4,25-28] "The facts [suggest] that the neonatal period is the most favorable time for the development of kernicterus and, moreover, that a brain lesion may develop at a lower concentration of bilirubin in the serum of prematurely born infants than in those born at term...."[28]

DIAGNOSIS

The serum level of the enzyme glutamic oxalacetic transaminase (GOT) is elevated in certain pathologic conditions, but presumably, because of the integrity of the BBB, there is no concomitant increase in the c.s.f. GOT.[29] Since the BBB "insulates" spinal fluid activity from systemic changes, spinal fluid transaminase levels have diagnostic value which, in certain states,[30,31] aids "...in the diagnosis and prognosis of cerebral infarction and may be helpful in differentiation of vascular from neoplastic lesions."[32] An experimental validation of the relationship between GOT levels and brain injuries is illustrated in fig. 4.

Fig. 4 Levels of GOT in Spinal Fluid of an Animal



Adapted from Smith, S. E., *et al.*[31]

METABOLIC AND ENDOCRINE CONSIDERATIONS

The conceptual barrier proves its clinical validity in the metabolic area in the study of glucose. "When the arterial blood glucose falls below 50 mg. %, cerebral dysfunction and coma are likely to result...."[33] Although the blood level is apparently

in excess of glucose requirements, the glucose concentration is not sufficiently high to enable this substance to traverse the BBB at a rate that will ensure normal metabolism.[33]

There is some evidence that hormones affect the permeability of the barrier to other substances.[34] Although in disease the barrier may become permeable to pituitary and adrenocortical hormones, their direct effect on brain metabolism in normal states has not been established.[35] The elevated c.s.f. protein found occasionally in Cushing's syndrome[36] suggests an altered permeability.

The role of the so-called neurohumors and their relationship to mental illness is as yet incompletely understood. Though formed from 5-hydroxytryptophane which does get across the BBB,[37] the difficulty[38] or inability[39] of serotonin to pass the barrier compels consideration of the BBB in psychopharmacologic investigation.

NEUROSURGERY AND NEUROPATHOLOGY

As a result of altered permeability permitting delineation of the neoplasm by intravenous injection of radioactive elements, the diagnosis and localization of brain tumors have been facilitated.[2] In the area of research, little understood disorders—such as the degenerative and demyelinating diseases—and the pathophysiology of cerebral vascular disorders are receiving greater illumination by useful exploitation of the BBB principle.[2]

PSYCHIATRY AND PSYCHOPHARMACOLOGY

The therapeutic effectiveness of a drug is "...to some degree a function of its availability in the target organ...[and may therefore be considered dependent] on the blood-brain barrier which controls the access of pharmacological agents to the central nervous system."[40] That this barrier may be modified experimentally has been previously noted.

Therapeutically, increasing the permeability of the BBB by the modalities of fever and ECT is known "...to facilitate the passing of chemical substances from the circulatory system into the brain and the surrounding cerebrospinal fluid."[40] In the psychopharmacologic treatment of depressions, this has reduced the "time lag" of therapeutic effect.

CONCLUSION

The access of a chemical agent to the brain must precede its pharmacodynamic effects. The blood-brain barrier evidently provides a buffering mechanism, whereby the internal environment is protected from physical insults and chemical "perturbations."[10] Variations in this mechanism may be reflected in the states of health or disease of the CNS[5] and influence the response to therapy.[7,40] The gaps in our knowledge of the vital blood-brain barrier should provide the stimulus for further investigation of this provocative concept.

Bibliography: (1) Editorial: The Blood-Brain Barrier, Lancet *2*:29, 1955. (2) Bakay, L.: The Blood-Brain Barrier, Springfield, Ill., Thomas, 1956. (3) Whipple, G. H., *et al.*: J. Exper. Med. *101*:617, 1955. (4) Driscoll, S. G., and Hsia, D. Y.: Pediatrics (supp.) *22*:785, 1958. (5) Tschirgi, R. D.: Biology of Mental Health and Disease, New York, Hoeber, 1952, pp. 34-53. (6) Bakay, L., in Richter, D.: Metabolism of the Nervous System, New York, Pergamon, 1957, pp. 136-152. (7) Holmes, J. H., and Tower, D. B., in Elliott, K. A. C.; Page, I. H., and Quastel, J. H.: Neurochemistry: The Chemical Dynamics of Brain and Nerve, Springfield, Ill., Thomas, 1955, pp. 274-293. (8) Brierley, J. B., in Richter, D.: Metabolism of the Nervous System, New York, Pergamon, 1957, pp. 121-135. (9) Ranson, S. W., and Clark, S. L.: The Anatomy of the Nervous System: Its Development and Function, ed. 10, Philadelphia, Saunders, 1959, pp. 71-88. (10) Livingston, R. B., in Ruch, T. C., and Fulton, J. F.: Medical Physiology and Biophysics: Howells' Textbook of Physiology, ed. 18, Philadelphia, Saunders, 1960, pp. 889-902. (11) Bakay, L.: A.M.A. Arch. Neurol. & Psychiat. *70*:30, 1953. (12) Lieberman, J., *et al.*: New England J. Med. *257*:1201, 1957. (13) Chou, S. N., *et al.*: A.M.A. Arch. Surg. *63*:554, 1951. (14) Lajtha, A.: J. Neurochem. *1*:216, 1957. (15) Lee, T., and Hsia, D. Y.: J. Lab. & Clin. Med. *54*:512, 1959. (16) Aird, R. B., *et al.*: A.M.A. Arch. Neurol. & Psychiat. *75*:371, 1956. (17) Bassett, R. C.; Rogers, J. S.; Cherry, G. R., and Gruzhit, C.: J. Neurosurg. *10*:38, 1953. (18) Lourie, H.; Weinstein, W. J., and O'Leary, J. L.: J. Nerv. & Ment. Dis. *130*:1, 1960. (19) Chambers, R., and Zweifach, B. W., cited in Bakay, L.: (ref. 2), p. 25. (20) Friedemann, U.; Mayer, S. E., and Bain, J. A.; Niessing, K.; Spatz, H.; Walter, F. K., cited in Arioka, I., and Tanimukai, H.: J. Neurochem. *1*:311, 1957. (21) Gerard, R. W., in Elliott, K. A. C.; Page, I. H., and Quastel, J. H.: *op. cit.* (ref. 7), p. 478. (22) Langworthy, O. R.: Am. J. Psychiat. *113*:597, 1957. (23) Katzenelbogen, S.: The Cerebrospinal Fluid and Its Relation to the Blood, Baltimore, Johns Hopkins Press, 1935. (24) Carter, C. H.: Current M. Digest *37*:61, 1960. (25) Morison, J. E.: Foetal and Neonatal Pathology, London, Butterworth, 1952, pp. 166-167. (26) Stempfel, R., and Zetterström, R.: Pediatrics *16*:184, 1955. (27) Vogel, F. S.: abstract, Am. J. Path. *29*:582, 1953. (28) Ernster, L.; Herlin, L., and Zetterström, R.: Pediatrics *20*:647, 1957. (29) Myerson, R. M.; Hurwitz, J. K., and Sall, T.: New England J. Med. *257*:273, 1957. (30) Miyazaki, M.: J. Nerv. & Ment. Dis. *126*:169, 1958. (31) Smith, S. E.; Cammack, K. V.; Dodds, M. E., and Curry, G. J.: Am. J. Surg. *99*:713, 1960. (32) Green, J. B., *et al.*: Neurology *7*:313, 1957. (33) Fazekas, J. F., and McHenry, L. C., Jr.: M. Science *8*:434, 1960. (34) Grenell, R. G., and McCawley, E. L.: J. Neurosurg. *4*:508, 1947. (35) Editorial: Mental Disorders Due to Corticotrophen and Cortisone, Lancet *2*:29, 1955. (36) Trethowan, W. H., and Cobb, S.: A.M.A. Arch. Neurol. & Psychiat. *67*:283, 1952. (37) Fazekas, J. F.: Am. J. Med. *25*:89, 1958. (38) Editorial: Serotonin and Psychiatric Illness, J.A.M.A. *173*:742, 1960. (39) Udenfriend, S., *et al.*: cited in Fazekas, J. F.: *op. cit.* (ref. 39). (40) Lehmann, H. E.: Am. J. Psychiat. *117*:356, 1960.

newer significance of the extrapyramidal system

INTRODUCTION

Although the neurologic disorders associated with the extrapyramidal system are included in this brain function study, this is not an exposition of the neurologic symptoms only, but is concerned also with some of the psychiatric aspects of extrapyramidal disorders.

With recent experimental techniques, the role of some of the extrapyramidal structures has had to be revised.[1] Neurosurgical relief of parkinsonism and hyperkinetic disease—heretofore "hopelessly progressive" states[2]—and the occurrence of parkinson-like symptoms which have been observed with certain tranquilizers, have helped highlight the extrapyramidal system as a borderline province of neurology and psychiatry. The manifestations of Parkinson's disease, in themselves, may frequently be attributed to mental illness. Thus the erroneous diagnosis of the initial fatigue as "neurasthenic" or of the emotionally geared tremor as part of "hysteria" is not infrequently made. On the other hand, the immobility and silence of the rigid parkinsonian facies may closely simulate, and be diagnosed as, a true endogeneous depression.[3]

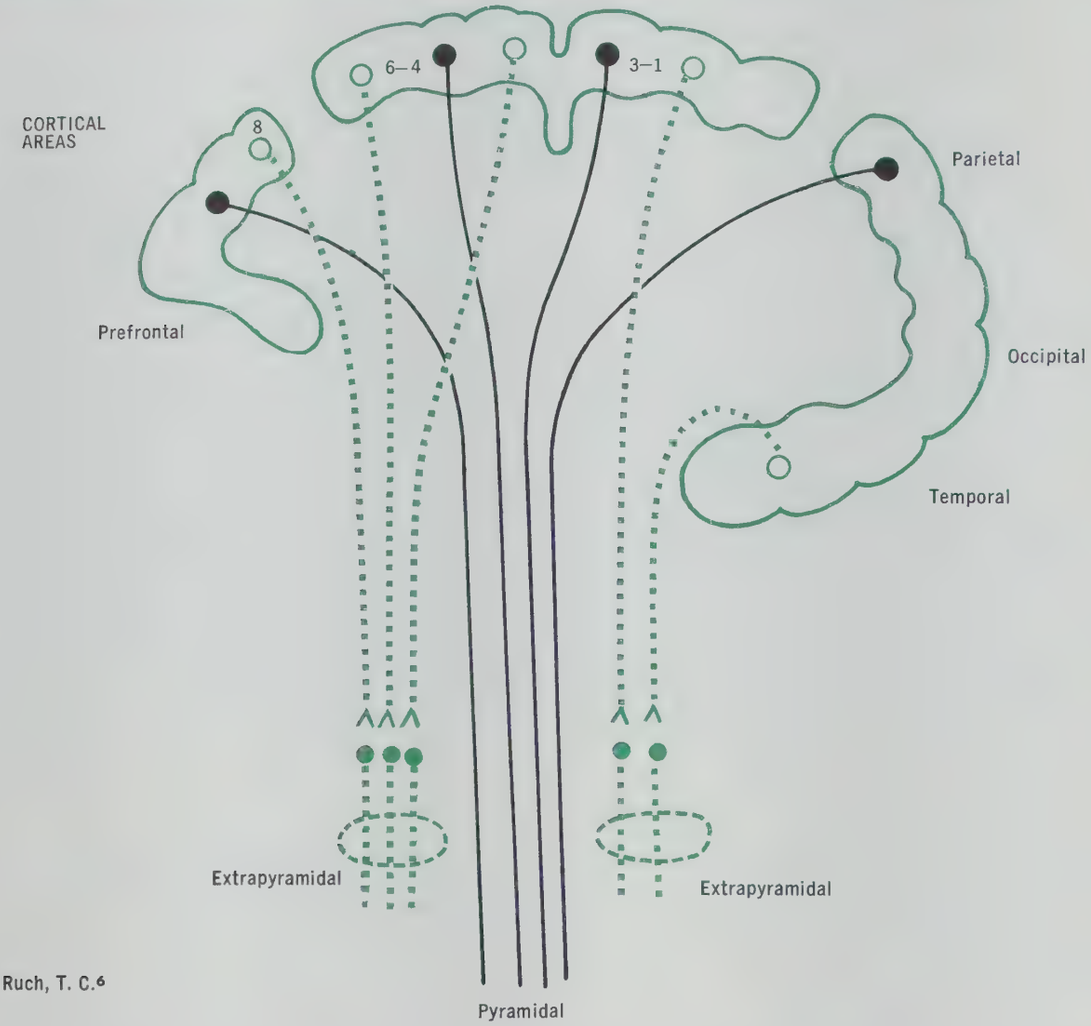
THE EXTRAPYRAMIDAL SYSTEM—GENERAL CONSIDERATIONS

DEFINITION

There is no universal acceptance as what the term "extrapyramidal" includes.[1,4] It is difficult to define since it is not a clear-cut anatomical entity. It includes the motor mechanisms of the central nervous system excluding those of the pyramidal tract[1]—in the broadest sense, "all nonpyramidal" motor systems.[1,5]

The classic division of discretely separate pyramidal and extrapyramidal tracts—each homogeneous and unlike the other—has undergone increasing modifications.[6] Both anatomically and physiologically this division has become less precise. Thus, some corticospinal fibers traversing the pyramids of the medulla are part of the so-called extrapyramidal system[1,7] and the "pyramidal" area of the cortex is now recognized as giving rise to efferent fibers other than those going to the anterior horn cells of the spinal cord. It thus appears that "... every motor cortical area ... [has] mixed pyramidal and extrapyramidal functions."[1]

Fig. 1 Diagrammatic Representation Showing Overlapping Origin of Pyramidal and Extrapyramidal Fibers



Adapted from Ruch, T. C.[6]

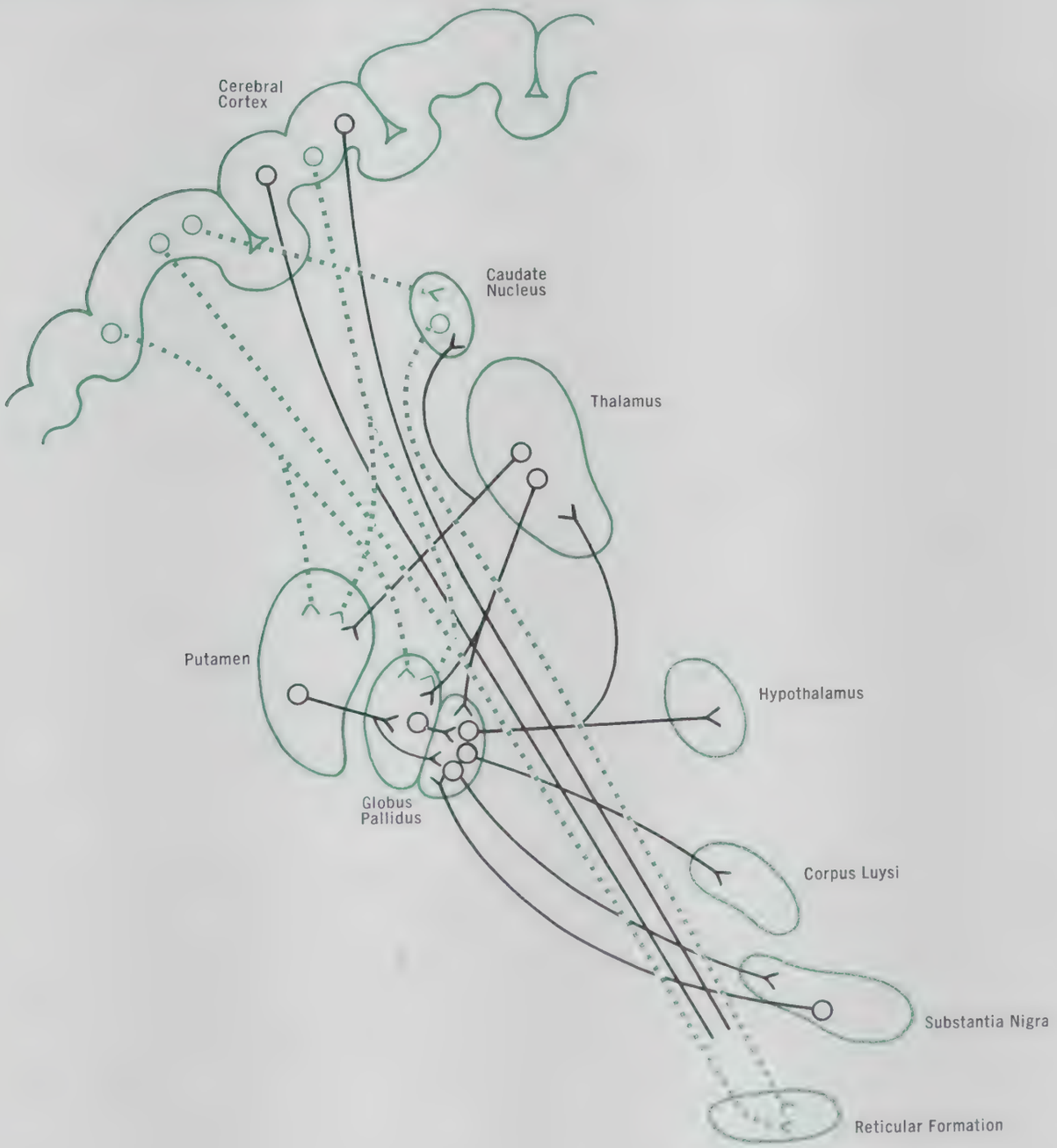
ANATOMY

Implicit in the foregoing is the great variation of structures included in the extrapyramidal system.[1] According to Krieg,[5] the term extrapyramidal includes the following heterogeneous group of neural structures: Extrapyramidal areas of cerebral cortex, thalamic nuclei connected with striatum, corpus striatum (including caudate, putamen, and pallidus), subthalamus, rubral system, and the reticular system. These structures are all loosely connected by a multiplicity of tracts creating a functional, rather than an anatomic unit.[7] Although reaching segmental distribution as does the pyramidal tract, the extrapyramidal tract differs significantly from the direct route of the former. There are many detours, and neuronal chains are synaptically interrupted in the basal and other subcortical ganglia and in the reticular system.[6]

Basal Ganglia — The basal ganglia are the subcortical motor nuclei of the forebrain. Of these, the putamen and caudate nucleus putamen are the highest subcortical centers in the extrapyramidal system.

These nuclei, forming the striate body, are the highest neural centers in lower forms—harboring the feeding, mating, nesting and migrating instincts.[5,7] Substantiating perhaps its phylogenetic role is the extensive development of the caudate nucleus and putamen in humans with cortical congenital abnormalities.

Fig. 2 Schematic Diagram of Structures and Some Interconnections of the Extrapyramidal System



Adapted from Ruch, T. C.[6]

PHYSIOLOGY AND PATHOPHYSIOLOGY

The extrapyramidal system functions generally to provide a background motor pattern of posture (and locomotion) on which the pyramidal system adds the nonpostural movements which form the basis of acquired skills.[7] This system evidently provides a facilitation of impulses passing from higher centers to lower motor neuron cells of agonist muscles, while suppressing the activity of the antagonist muscles. The findings of comparative physiology, already mentioned under basal ganglia, suggest a relation to instinctive behavior. The extrapyramidal centers "...contain the motor mechanisms of attentive behavior and of the postural accompaniments of wakefulness in close coordination with the reticular formation of the brain stem."[1] To attribute special functions to individual nuclei, however, would be an oversimplification. For in spite of the many studies, very little is known of how the extrapyramidal system performs its function or of the coordinated action of its parts.[1]

METHODS OF STUDY

Unfortunately, basal ganglia lesions in humans are produced mainly by diffuse pathologic processes so that clinical cases (or post-mortem studies[5]) tell little of functional localization.[4,8] One reason for the difficulty in visualizing the normal function of basal ganglia lies in the inadequacy of the conventional experimental methods—ablation, stimulation and degeneration—for providing essential information.[6] Another may be attributed to phylogenetic differences—and differences in motor organization—which do not permit valid application of the results of animal experimentation to humans.[5]

The simulation of some human conditions by animal experiments, however, does permit speculation as to genesis of extrapyramidal disease states. Thus Magoun[9] has been able to reproduce parkinsonian-like symptoms in monkeys by localized lesions in the brain stem. From his observations he suggested that parkinsonian hypokinesis might be attributable to impairment of facilitatory influence of the extrapyramidal system. Similarly, conditions simulating hemiballism and parkinsonian tremor have been produced in monkeys by damage to the subthalamic nucleus and substantia nigra, respectively.[5]

Stereotactic methods of explanation in animals[5] and man[10] have provided the investigator with some clarification of the role of the basal ganglia in extrapyramidal disorders. Since electroencephalograms only serve to record surface currents, depth encephalography has been utilized to provide some information as to the functional state of basal ganglia in disease and under the influence of drugs. Operative procedures, as will be observed below, provide us with still additional information.[3,9,11,12] Nevertheless, the problem of pathophysiology is still obscure.

THE CLINICAL PICTURES

SYMPTOMATOLOGY

Clinically, "extrapyramidal" disease (since no pyramidal fibers are involved) is evidenced as

abnormalities of muscle function. These may be involuntary movements, loss of movement, or aberrations in muscle tone, *i.e.*, rigidity, spasticity or hypotonia.[7] These may occur separately or in combination.[13]

The classical extrapyramidal syndrome—parkinsonism—exemplifies the two most important clinical extrapyramidal signs of rigidity and tremor.[6] It is classified as 1) hypokinetic or rigid syndrome, and 2) the hyperkinetic, dystonic syndrome, which includes choreic, athetoid, ballistic, myoclonic and dystonic syndromes.[1]

LESIONS

In some instances, evidence indicates a specific pathological site as, for example, the subthalamic nucleus in ballism. Generally, however, "Clinical and pathologic observations, animal experiments and neurosurgical attempts to relieve chorea and athetosis have not yielded any consistent picture of the underlying mechanism of these diseases and what lesions produce them."[6] Destruction of nerve cells in the substantia nigra has been suggested as the anatomical defect in the parkinsonian syndrome,[1] but symptomatic improvement with diverse surgical procedures[2,6,12] leaves the mechanism still obscure.

Improvement of extrapyramidal symptomatology following surgical therapy has bordered on the dramatic,[3,11] although results with modern stereotactic operations are at variance with classical neurophysiology. To illustrate, both stimulation and extirpation of the same striate area will relieve parkinsonian tremor. Especially at odds with orthodox teachings is the more reliable control of the involuntary movements achieved following surgical lesions of the ventromedial nucleus of the thalamus than with those obtained by lesions involving the globus pallidus.[3,14]

Bilateral thalamotomy also has relieved hypertonic and hyperkinetic manifestations.[11] The newer neurosurgical procedures have thus aided the study and localization of function but have not clarified the mechanisms involved.

ETIOLOGICAL AND OTHER CONSIDERATIONS

Some aspects of parkinsonism, by far the most prevalent of the extrapyramidal disorders, are presented for consideration here. Doshay believes that Parkinson's disease is a "distinct disease entity" and that the idiopathic type "...is the only true form of Parkinson's disease."[15] Although the cause is unknown, Doshay considers a separation between the "so-called" arteriosclerotic and idiopathic types as purely artificial. The fact that exogenous chemicals (drugs) have produced symptoms resembling parkinsonism supports Doshay's theory of "...some as yet unidentified chemical substances that are manufactured within the body..."[15] affecting certain brain cells and causing the idiopathic form.

That there is more than a neurologic stratum for parkinsonism has been commented upon by several investigators.[16-19] Grinker and Spiegel[17] have reported "full-blown Parkinson's syndrome" in patients with acute combat neurosis. Based on his observations of 12 leucotomies, Oliver[18] reported that the aim of this procedure was not to abolish tremor but rather to relieve "...patients

from episodes of mental tension..." which aggravate manifestations of the disease. Jeliffe[19] has commented on the similarity of the "catalepsies" in parkinsonism and catatonia. These considerations confer a special significance to the drug-induced parkinsonism manifestations which have at least a theoretical relationship to the foregoing.[16,20]

EXTRAPYRAMIDAL DRUG EFFECTS CONSIDERATIONS

The true worth of the tranquilizers is evidenced by the fact that the discharge rate of psychiatric patients has exceeded the admission rate since 1955—the year these drugs were first employed.[21] However, the therapeutic use in psychotics of the major tranquilizers—the phenothiazines and reserpine—frequently has been accompanied by neurologic effects characteristic of extrapyramidal involvement.[22] With certain types of phenothiazines the incidence of these reactions in high dosage may exceed 40 per cent.[22,23] Fortunately these are readily reversible. Generally, it appears that those compounds which do not elicit the extrapyramidal effects show least beneficial effect on the symptoms treated.[23] Although there is some disagreement[23,24] as to correlation between extrapyramidal symptoms and therapeutic efficiency, one investigator[25] considers parkinson-like activity an index of the therapeutic effect of these agents.

A higher incidence of extrapyramidal effects has been reported in females[23,24] although dyskinesia and akathisia occur predominantly in males.[22] All ages may be affected. The diagnosis is not difficult if the possibility of extrapyramidal drug effects is kept in mind. A positive urinary test for phenothiazine metabolites corroborates the diagnosis when history is indefinite.[24] It is important to note that although "the prevalent opinion seems to be one of relative unconcern..."[26] in rare instances more severe reactions have been reported.[26]

TYPES OF EXTRAPYRAMIDAL REACTIONS

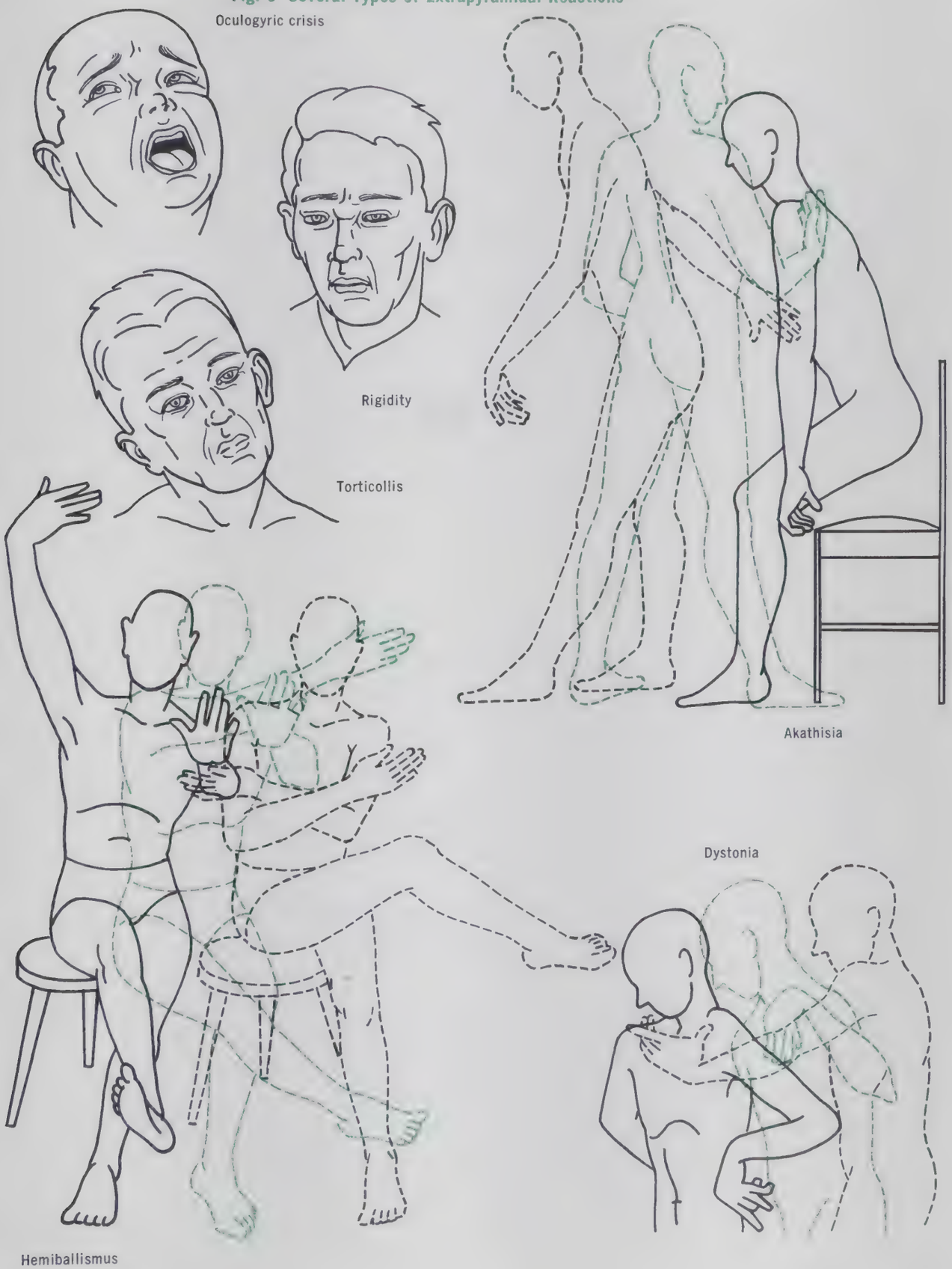
Generally, the reactions encountered are reversible and not hazardous.[26] Nevertheless, in appearance, these neurologic side effects may be most disturbing to the physician as well as to the patient and his family. Some of the erroneous tentative diagnoses—*i.e.,* tetanus, encephalitis, meningitis, rabies and botulism—reflect the bizarre symptomatology encountered.[24]

The drug-induced extrapyramidal reactions may be divided into three groups:[22,23]

1. *Parkinsonism or Parkinsonian-like Reactions*—Characterized by gait and postural abnormalities, rigidity, tremor and salivation. Not all patients developing this type reaction will exhibit the full-blown syndrome. Onset of symptoms varies with drug and dosage used. Symptoms generally appear during the first eight days and may at times be related to change in dosage or to new route of administration (*i.e.,* oral to parenteral).[22]

2. *Dystonia or Dyskinesia*—These are spasms or cramps of muscles which may be restricted to a single muscle or occur in various combinations.[22,23] Trismus, torticollis, mandibular tics, torsion spasms, oculogyric crisis, opisthotonus, forced protrusion of tongue and risus sardonicus have all been described. The dyskinetic reaction has a more rapid onset (after 2 to 3 days' therapy) than

Fig. 3 Several Types of Extrapyramidal Reactions



the parkinsonism-like reactions and this difference may be attributed to "...different locations of biochemical action within the extrapyramidal system."[24]

3. *Akathisia*—This is a specific syndrome characterized by a "motor restlessness."[22] It shows a great deal of variation in degree. The patient's feelings may vary from one of being driven, to complete "...inability to sit down and keep still."[23]

MANAGEMENT OF DRUG REACTIONS

In general these extrapyramidal reactions are not difficult to handle and are readily reversible. In some instances lowering dosage will control them. Reassurance of the patient and the administration of antiparkinsonism drugs have been successful in controlling most reactions. In more severe reactions, caffeine sodium benzoate intravenously[24] has been effectively employed. Where reaction occurs in psychiatric cases, combining an antiparkinsonism drug with a lower dosage of tranquilizer can often permit continuation of therapy.[24] "Implicit in all the above is the indication that no drug will be given except when necessary, that no tranquilizer, powerful neuroleptic, or stimulant drug will be given when a simpler drug will suffice, and that the dosage level of the drug used will be appropriate to the symptomatology or target symptom that one is attempting to control."[22]

THEORETICAL SIGNIFICANCE

Drug-induced extrapyramidal reactions are neurologically determined and considered to be due to "...the effect of these drugs on the basal ganglia and their connections."[22] That these are neurophysiological concomitants of neuroleptic activity, rather than toxic reactions, has been indicated by several studies.[27,28]

Some of these extrapyramidal reactions, in themselves, are strongly suggestive of psychiatric syndromes. Thus, if the physician is not wary, the erroneous diagnosis of conversion hysteria may be made, and may result in the danger of increasing the phenothiazine dosage.[24] Catatonic-like states following phenothiazines have been reported in the literature.[29] The occurrence of decreased motor activity, negativism, catalepsy,[30] hyperkinesis and autonomic phenomena characteristic of this type of schizophrenic reaction with phenothiazines supports the theory of chemical production of schizophrenic states. Brodie[31] and associates interpret this as a blockage of norepinephrine and an increased liberation of serotonin (5-hydroxytryptamine). This mechanism has been demonstrated to produce a catatonic picture in animals.[32]

Another observation[22] of psychiatric consequence is the predisposition of certain personalities to psychodynamically determined behavioral reactions of a "paradoxical" type when exposed to certain drugs. In this schema, this is considered to be an interaction of the pharmacologic profile of the drug with the patient's psychologic reaction type. Although the concept of pharmacologic sensitivity is still barren, it has been suggested that parkinsonian akinesia may be a neurochemical result "...in service of ego-homeostasis."[20] In some instances it may thus serve to dam up a threatening acting out of aggressive impulses.

Since the genesis of drug-parkinsonism on purely neural factors has been found wanting,[20] an

interaction between neural and psychic factors—a mysterious borderline region—presents a fruitful area for further investigation.

EVALUATION AND CONCLUSION

The discussion presented has indicated the interdependence of the various motor brain areas and has presented the theory that damage to one of these brain areas interferes with functional integrity of the brain.[1,13,33]

The harmonious cooperation between cerebral cortex and extrapyramidal system is apparently "...one of the most essential elements in normal psychomotor activity."[13] Serious mental disturbances are often expressed by extrapyramidal mechanisms with dominate cortical functioning. The catatonic schizophrenic frequently mimics the parkinsonian state with his facial grimacing and muscular rigidity. That there is a correlation between mental disease and the extrapyramidal disorders is illustrated by the abnormal muscular movements observed in schizophrenic hysteria, dementia paralytica and other abnormal conditions. "It would seem then that profound disturbances in an individual's mental life may express themselves by utilizing extrapyramidal mechanisms which apparently have gained dominance over cortical functioning."[13]

Interest in the extrapyramidal system has received renewed impetus as a natural consequence of the success of diverse neurosurgical techniques, as well as of the advent of psychopharmacologic drugs with the attendant consequence of drug reactions simulating extrapyramidal disorders.

Bibliography: (1) Jung, R., and Hassler, R., in Field, J., *et al.*: Handbook of Physiology, Section 1: Neurophysiology, vol. 2, Washington, D. C., American Physiological Society, 1960, pp. 863-928. (2) Cooper, I. S.: Ann. Int. Med. *45*:381, 1956. (3) Miller, H.: Practitioner *184*:170, 1960. (4) Ranson, S. W., and Clark, S. L.: Anatomy of the Nervous System: Its Development and Function, ed. 10, Philadelphia, Saunders, 1959, pp. 317-318. (5) Krieg, W. J. S.: ed. 2, Functional Neuroanatomy, New York, McGraw-Hill, 1953, pp. 296-298, 333-335. (6) Ruch, T. C., in Ruch, T. C., and Fulton, J. F.: Howell's Textbook of Physiology, ed. 18, Philadelphia, Saunders, 1960, pp. 249-284. (7) House, E. L., and Pansky, B.: A Functional Approach to Neuroanatomy, New York, McGraw-Hill, 1960, pp. 329-352, 426-428. (8) Wechsler, I. S.: A Textbook of Clinical Neurology, ed. 7, Philadelphia, Saunders, 1952, pp. 564-566. (9) Magoun, H. W., cited in Doshay, L. J.: *op. cit.* (ref. 15). (10) Spiegel, E. A.; Wycis, H. T.; Baird, H. W., III, and Szekely, E. G.: A.M.A. Arch. Neurol. & Psychiat. *75*:167, 1956. (11) Krayenbühl, H., and Yasargil, M. G.: J. Nerv. & Ment. Dis. *130*:538, 1960. (12) Cooper, I. S., *et al.*, in St. Barnabas Symposium on Surgical Therapy of Extrapyramidal Disorders, J. Am. Geriatrics Soc. *4*:1-151, 1956. (13) Keschner, M., in Tice, F., and Sloan, L. H.: Practice of Medicine, vol. 10, Hagerstown, Md., Prior, 1959, pp. 307-318. (14) MacCarty, C. S.: Proc. Staff Meet. Mayo Clin. *34*:343, 1959. (15) Doshay, L. J.: J.A.M.A. *174*:1962, 1960. (16) Guggenheim, P., and Cohen, L. B.: Psychosom. Med. *20*:151, 1958. (17) Grinker, R., and Spiegel, J., cited in Guggenheim, P., and Cohen, L. B.: *ibid.* (18) Oliver, L. C.: Parkinson's Disease and Its Surgical Treatment, London, Lewis, 1953. (19) Jeliffe, S. E., cited in Guggenheim, P., and Cohen, L. B.: *op. cit.* (ref. 16). (20) Guggenheim, P., and Cohen, L.: Dis. Nerv. System *20*:1, 1958. (21) Benson, W. M., and Schiele, B. C.: Journal-Lancet *80*:579, 1960. (22) Sarwer-Foner, G. J.: Canad. M. A. J. *83*:312, 1960. (23) Freyhan, F. A.: Am. J. Psychiat. *115*:577, 1959. (24) Cain, H. D., and Malcolm, M.: California Med. *93*:24, 1960. (25) Goldman, D.: Am. J. M. Sc. *235*:67, 1958. (26) Tytus, J. S.; Gofarth, E. G., and Ogle, W.: Bull. Mason Clin. *13*:9, 1959. (27) Haase, H. J., cited in Freyhan, F. A.: *op. cit.* (ref. 23). (28) Freyhan, F. A.: A.M.A. Arch. Neurol. & Psychiat. *78*:465, 1957. (29) May, R. H.: Am. J. Psychiat. *115*:1119, 1959. (30) Berry, R. V.; Kanin, S. H., and Kline, A.: U. S. Armed Forces M. J. *9*:745, 1958. (31) Brodie, B. B., *et al.*, cited in May, R. H.: *op. cit.* (ref. 29). (32) Sacchi, U., *et al.*, cited in May, R. H.: *op. cit.* (ref. 29). (33) Himwich, H. E.: J. Nerv. & Ment. Dis. *130*:505, 1960.

concepts of aphasia

INTRODUCTION

DEFINITION AND SCOPE

By exploring speech—its reception, manipulation and expression—investigators and clinicians are developing an increasing awareness of the brain and its intricate mechanisms. Involvement of the understanding, reading, speaking or writing of language, individually or in any combination, may be designated as aphasia.[1] "It does not refer to a defect in the mechanics of hearing and speaking, but to an impairment of the highest function of the use of language, interpretation, and translating thought."[2] Though aphasia occurs in some psychotic patients with diffuse brain lesions, Wechsler[3] believes that aphasia is neither a mental nor a personality defect.

Conrad[4] has described the patient with sensory aphasia thus: "He experiences certain sensations of speech which do not reach the level of comprehension... only outlines which surround a diffused core are grasped; the sounds of speech fluctuate; they appear to become extinct too fast for the patient; again and again he asks for a repetition of what has been said. Briefly, he behaves like the [healthy] individual in front of the tachistoscope. And even if he understands correctly, there remains the element of non-finality, he cannot get rid of the feeling that he cannot really understand what he has been told, but is only guessing. He is forced to concentrate, as in an environment the language of which is foreign, and the moment he slackens his concentration he loses all connexion."[4]

Fig. 1 Symbolic Representation of the Aphasic Patient.

CLASSIFICATION AND TERMINOLOGY

Stated simply, aphasia is "...a primary disorder of the reception, manipulation, and expression of language."[5] The precision of classification into diverse subgroups and categories is not at all indicative of the dynamics at work nor of the clinical cases encountered, since a categorized case is a rarity.[6] Classification serves merely to systematize.[7] In the broad clinical sense physicians may recognize the following aphasic types:[8]

Receptive—comprehension is primarily involved

Expressive—difficulty in the expression of language

Expressive-Receptive—equal involvement in both spheres

Global—absence of language capacity in any area of communication

In some degree further subdivisions of aphasia reflect the investigator's preconceptions of language and aphasia.[9] Auditory aphasia (word deafness) and visual aphasia (defect in seeing and understanding written language) together compose the classical sensory aphasia of Wernicke.[3] The defect in uttering words is often referred to as the motor aphasia of Broca. Agraphia (defect in writing), amusia (loss of ability to sing), amimia (inability to mimic), amnestic aphasia (loss of memory for words) have all been recognized.[3] Bucy[10] employs the terms aphemia and anarthria (disturbances of speech) and alexia (word blindness). A partial aphasia has been designated as paraphasia. In children, "Some specialists prefer to use the term *dysphasia* to indicate a partial problem...."[11] The extent of descriptive terminology employed indicates the subtlety of the problem. Rather than be used to designate specific speech involvement, aphasia is better envisaged as a concept.

HISTORICAL DEVELOPMENT WITH COMMENTS

Past—Although the concept of aphasia is still evolving, the entity has a long history. Hippocrates mentioned "aphonia" in his writings. Later observers of this clinical state were Schmidt (1676) on alexia, Rommel (1683) on motor aphasia, and Gesner (1770) on jargon aphasia.[12] As Critchley[13] and Schuell[14] state, an historic advance was made one hundred years ago when the surgeon-anthropologist Broca reported on two patients with problems of speech, which he labeled aphemia.

As Schuell[14] points out, Broca emphasized the importance of localizing speech faculties according to the brain convolutions.[14] The nineteenth-century investigators have been characterized[15] as "diagram makers," for they concentrated on the delineation of exact functional areas. In this "mosaic theory of cortical function,"[14] for example, the frontal lobe was presumed to contain cells carrying images of movements of speaking words and the cells of the temporal lobe as carrying images of word sounds. A specific aphasic disorder was thus presumed to follow destruction of a specific area and to be related to that area alone.

Present—Freud[16] rejected the concept of centers and static faculties and spoke in terms of fields and dynamic processes. Critchley[13] points out that Hughlings Jackson was the first neurologist to adopt the dynamic attitude towards brain damage, that he considered himself "neither a universalizer nor a localizer," and that "...he deemed it incredible that 'speech' could 'reside' in any limited spot," since speech and words are part of thought. Much time was to elapse, however, before the dynamic formulation of the functional mechanism of the nervous system, as expressed by Head and Critchley, was to obtain fuller appreciation. Penfield and Roberts[17] are among the investigators who today are arrayed with those favoring the dynamic interpretation.

CLINICAL PICTURE

CAUSES OF APHASIA

Aphasia is generally attributed to organic lesions, although some investigators speak of a temporary hysterical etiology.[3,18] This damage may be a manifestation of tumor, inflammation, trauma, degenerative or vascular disease.[18] Solomon[19] has reported an unusual receptive aphasia associated with temporal lobe epilepsy. Congenital aphasia has also been reported.[20] In children, aphasia may result from cortical damage, insufficient cortical development or malfunction of the cerebral pathways; there may be a familial factor.[11] In discussing semantic aphasia, Riese[7] finds the major lesion in the left parieto-temporo-occipital areas.

THE APHASIC PATIENT

Aphasia is rarely seen in its "pure" form[10,18] and symptoms may lie anywhere between the extremes. Thus, in expressive aphasics a moderate word-finding impairment may be observed in one patient, mutism in another.[21] In addition there is a flexibility in the defect itself, which may vary according to the aphasic stage and the conditions confronting the patient.[7]

There are many curious varieties of aphasia. One patient may develop an anomic aphasia and be unable to name objects but can describe the actions of the examiner;[19] another individual may retain only a limited number of words with which he expresses his entire range of ideas. Automatic word series; e.g., counting, and reactive speech, "hello" or "goodbye," tend to survive.[6]

Emotional speech (i.e., ejaculations, swearing) may persist especially when propositional speech, for expression of ideas, is lacking.[10] In general the more abstract elements of common speech are lost most frequently and are the last to be recovered.[1] Symbolism other than speech may be included in the aphasic loss—telling time, reading maps, simple calculation.[1] The more erudite and educated patient who has developed abstract, subtle and symbolic language may thus have a greater aphasic deficit than the person of lesser intelligence suffering a lesion of similar location and extent.

EVALUATION AND REHABILITATION

Due to the nature of the underlying brain pathology which is thought to produce aphasia, other neurologic defects also may be expected to occur.[15] In the neurologic evaluation of the patient, visual, motor, hearing and sensory disorders can be found.[15] In this evaluation, audiometric testing is essential. Intelligence must also be carefully considered for prognosis.[2,5] Special tests have been devised to evaluate the aphasic patient and to measure his improvement. Schuell and Jenkins[15] employ combinations of perceptual, motor and language defects (see Fig. 2) to divide patients into five groups. Prognoses attached to these groups are quite consistent. Another guide to prognosis may be obtained with the electroencephalogram.[22]

Fig. 2 Types of Tests Employed to Evaluate Aphasic Patients.*

Speech and Language Deficit

1. Imitation of gross movements of speech musculatures
2. Rapid alternating movements of speech musculature
3. Repetition of monosyllables
4. Repetition of polysyllabic words and phrases
5. Sentence completion
6. Serial responses (counting, days of the week, etc.)
7. Response to questions
8. Naming pictures
9. Rhyming
10. Expressing ideas
11. Giving information
12. Definitions
13. Similarities
14. Retelling a paragraph

Visuo-motor and Writing Deficit

1. Copying forms
2. Drawing wheel, man
3. Writing letters to dictation
4. Writing words to dictation
5. Writing sentences of progressive length to dictation
6. Writing spontaneous sentences
7. Writing spontaneous paragraph describing a picture

Auditory Deficit

1. Recognizing letters
2. Recognizing objects
3. Pointing to objects named in a series of two or three
4. Following directions of progressive length
5. Recognizing errors in sentences
6. Paragraph comprehension
7. Auditory retention span
   (Repeating digit series and sentences of progressive length)

Visual and Reading Deficit

1. Matching forms
2. Matching letters
3. Matching pictures
4. Matching word to picture
5. Matching printed to spoken words
6. Sentence comprehension
7. Paragraph comprehension

*Adapted from The Minnesota Test for Differential Diagnosis of Aphasia, Research Edition, Form 7, by Hildred Schuell, Ph.D., Minneapolis, University of Minnesota Printing Dept., 1955. Used by permission of Dr. Schuell.

According to Hoerner and Horowitz,[8] there are some clinicians who regard rehabilitative measures in the aphasic as having no influence, attributing any recovery to "...reorganization processes of the residual cerebral functional capacity." However, these authors believe that "...such spontaneous restitution is of value to the patient only if controlled stimuli are applied to provide its integration and function."[8] Others[14,15] believe in controlled intensive auditory stimulation as the basis for treatment, much as language is originally learned. Rehabilitation depends on physical abilities, social surroundings and emotional status for "Aphasia involves more than a language problem... some symptoms may be due not to actual brain damage but rather to the patient's idea of 'self' and his status in life."[8] The depression and anxiety that results when a patient finds himself without speech can itself affect the language function. It should also be kept in mind that thoughtful, considerate nursing care is a basic part of rehabilitative therapy.[23,24]

CHILDREN WITH APHASIA

Diagnosis and treatment of aphasia in children are new areas of investigation. Strauss[25] differentiates between oligophasia, a lack of language development, and aphasia, "...loss of language after language has grown to its full expression as a communicative channel of thought...." It is especially important in children to differentiate aphasia from deafness, emotional illness, psychosis and mental deficiency.[11] The intellectual potential of the aphasic child usually is within normal range and the defect is related to cortical damage: "The aphasic child must be helped to *organize* incoming stimuli, so that they can be used more meaningfully for communication purposes."[11]

INVESTIGATIONS IN PATHOPHYSIOLOGY

EVOLUTION AND EXPERIMENTATION

Since "Man is the only animal which has developed articulate speech,"[1] the investigator of aphasia is hindered by his inability to employ animals in clarifying problems of speech localization.[10] In studies of conditioned reflexes in animals, disturbed symbolization has shown no cerebral localization. And, unlike the human brain, dominance of one cerebral hemisphere has not been demonstrated.[10] Lower animals—bees, birds, dogs and monkeys—may communicate but "...man alone has an inborn control mechanism for vocalization in his cerebral cortex."[17] And man alone apparently has the even more important neurological structures essential for ideational speech; i.e., the greatly increased temporo-parietal cortex that developed in the evolutionary passage from anthropoid ape to man.[17]

HUMAN STUDIES AND RESEARCH TOOLS

To a very large extent our knowledge of aphasia has depended heavily upon clinical material. It is not surprising, in view of the diversity and multiplicity of lesions associated with aphasia, that many contradictions and controversies exist.[10] Notwithstanding the general reliance on autopsy material for data, electrical stimulation of the exposed cortex during surgery[1] and, more recently, operative cortical excisions[17] are providing remarkable new information in mapping the speech regions of the cortex. Thus, when cortical areas 22 (syntaxis), 44 (verbalization) or 50 (semantics) are stimulated, speech is interrupted and objects cannot be named.[1] Mapping during an operation in which part of the temporal lobe was removed, is indicated in the accompanying figure.

Scientific contributions to the study of aphasia come from neurology, psychiatry, pediatrics, psychology, audiology and speech pathology.[11] New methods for the study of aphasic utterances, improved psychologic testing procedures and research into language are supplying valuable information.[13]

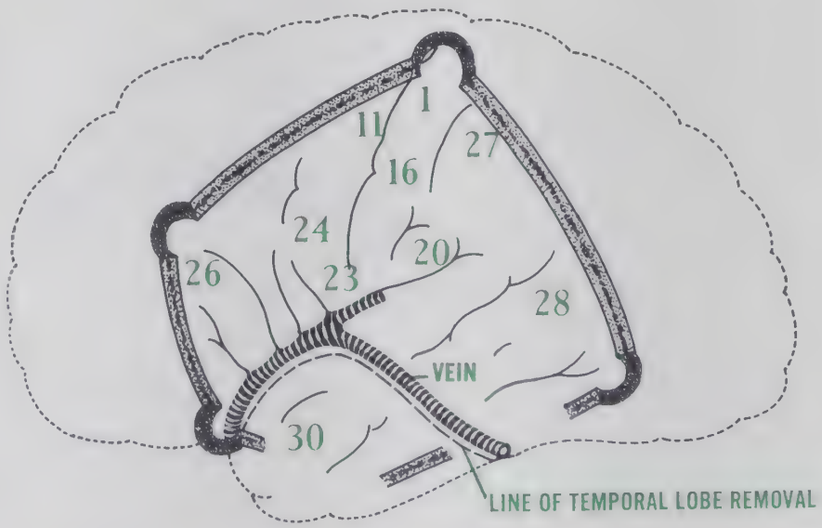


Fig. 3 Mapping of Speech Area in a Patient. Electrode Stimulation at Points 23 and 24 Produced Motor Speech Arrest. Stimulation at Points 26, 27, 28 Produced Aphasic Arrest.*

*Adapted from Penfield, W., and Roberts, L.: Speech and Brain-Mechanisms, Princeton, N. J., ©Princeton University Press, 1959.

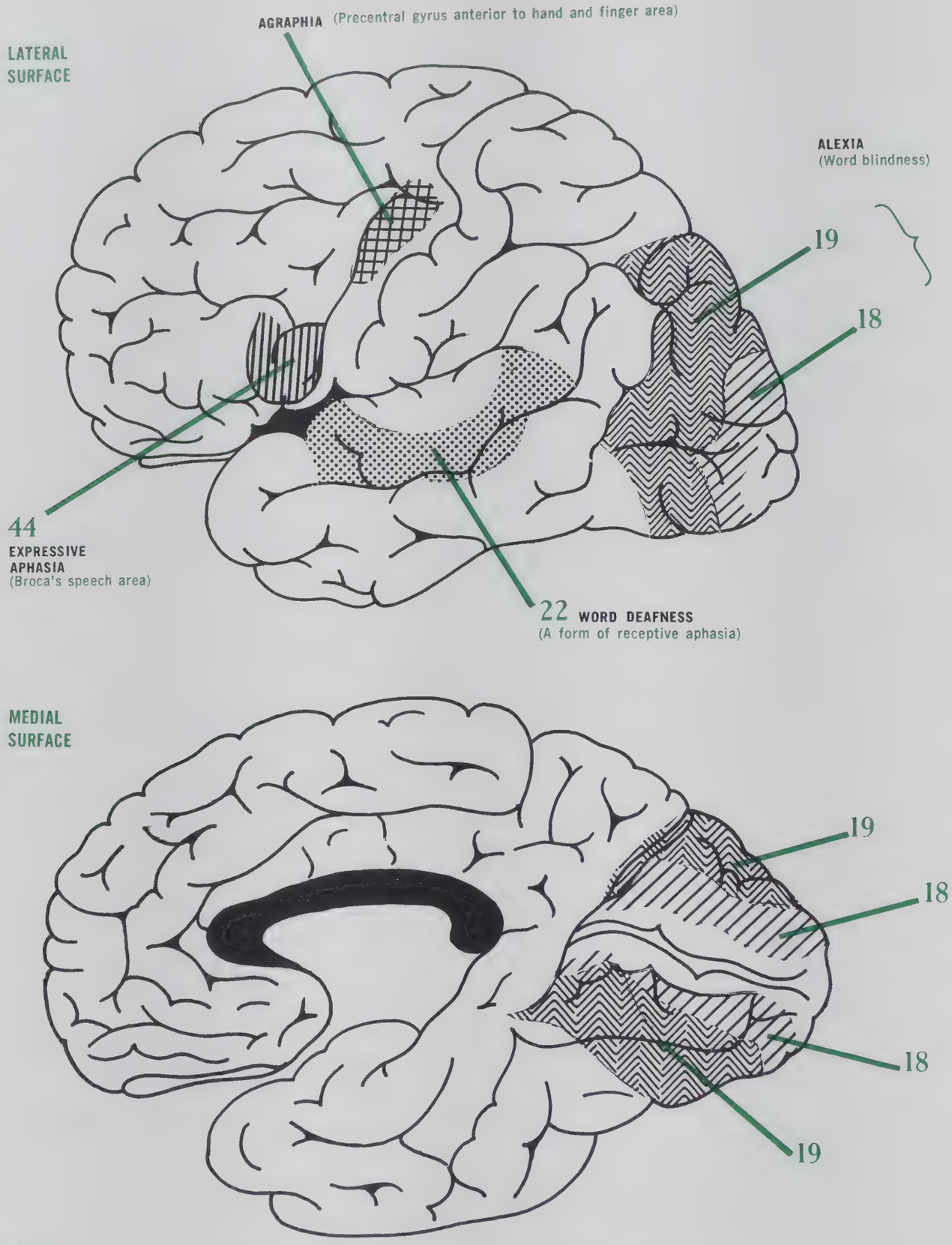


Fig. 4

An Interpretation of Localization of Cortical Language Areas as Related to Aphasia. Medial and Lateral Views of Cerebral Hemisphere.*

*Adapted from House, E. L., and Pansky, B.: A Functional Approach to Neuroanatomy, New York, © McGraw-Hill, 1960, pp. 431-433.

APHASIA AND CEREBRAL LOCALIZATION

What area or areas of the brain must be damaged to produce specific aphasic disturbances? Is the disturbance the result of damage to one area alone or is it a manifestation of the interference imposed upon the dynamics of the entire speech areas of the brain? As already indicated, ideas and opinions vary considerably: some investigators adhere strictly to speech localization, while others refer to a diffuse, uncircumscribed "field of speech."[4] However, certain circumscribed areas of the brain are generally recognized to have assignable speech relationships.[4]

Broca's region lies in the third left frontal convolution just anterior to the cortical representation of muscles of speech.[6] Similarly, word deafness—an inability to understand spoken language—has been attributed to parts of the temporal convolutions separate from, but contiguous to the cortical hearing center; word blindness is traceable to an area in the posterior parietal lobule contiguous to, but apart from the occipital visual area.[6] Thus, neuroanatomy confirms clinical observations of the independence of the sensorimotor and aphasic areas.

HANDEDNESS AND CEREBRAL DOMINANCE

Although its full significance is still not evident, the left cerebral hemisphere is generally dominant for speech.[17] Most aphasic patients present left cerebral lesions though the lesions have been seen in the right hemisphere in ambidextrous or left-handed patients.[10] In a child, damage to the posterior speech cortex may permit transfer of the speech mechanism to the opposite hemisphere.[17] The brain of a child is evidently more plastic than that of an adult: the adult may lose speech permanently following damage to the dominant hemisphere, while a child with a similar lesion may recover in a matter of months.[17]

THEORIES AND INTERPRETATIONS

Aphasia is viewed and interpreted differently by various investigators depending on background and training.[4] Though not clear cut, in general these interpretations may fall into two categories—neurologic and psycholinguistic.

NEUROLOGIC APPROACH

The "localized" versus "dynamic" controversy still persists, although localization is less significant today. Most investigators recognize the clinical types of aphasia attributable to certain lesions,[17] but, as Critchley[13] indicates, "The functional disturbance within the province of symbolic thinking is realized to be more complex and usually more intense than can be ascribed to the negative effect of a circumscribed lesion."

Krieg[1] notes that, in 1923, Head had recognized this complexity when he showed that aphasia was a disorder "...not of one or more of higher psychosensory areas developed in connection with the specific systems... but rather of loss of ability to evoke the complex symbolism necessary for speech comprehension or expression."[1] Krieg suggests that "asymbolia" would thus be a preferable term for aphasia.

Levin[26] sees developmental "links" that are formed between a center for the word and the neural patterns that underlie the corresponding image. An example of this pattern is the child's learning that an object of a given size, shape, color and aroma is an "orange." According to this theory, one may view aphasia as an impairment of these patterned links. Penfield[17] proposes a more neurologically definable speech hypothesis. He suggests that the "...three cortical speech areas in man are coordinated by projections of each to parts of the thalamus, and that by means of these circuits the elaborating speech is somehow carried out."

LINGUISTIC DEVELOPMENT

Krieg[1] sees language as "...a complex symbolism with several stages of integration and it is precisely these phases of synthesis that are isolated in the various types of aphasia...." From his observations, he concludes that the individual passes successively through several stages of language integration—*verbal, nominal, syntactic* and *semantic*. He states that the subtleties of difference between these stages may be recognized in the individual clinical case. Anatomically, these four developmental speech levels are "arranged from before backward" on the lateral cerebral surface.[1]

Riese[7] and other investigators see language as an *integrated* function (and not divided into isolated cortical components) with the individual drawing from *all* cerebral structures during his lifetime.

As supportive evidence for a single dimension of language deficit in all aphasias, Schuell and Jenkins[15] have shown that the language deficit in aphasia is apparently independent of other factors in a brain-damaged population. Thus, while over-all prognosis appears related to the injury, when language recovery occurs, it progresses independently of other defects.

GESTALT THEORY

Conrad[4] feels that the aphasic phenomenon can be viewed best psychologically as a disorder of gestalt formation; that is, as a lack of emergence of the gestalt. In this interpretation, normal speech is seen as a building up of gestalts. In the aphasic, these gestalts do not pass beyond the stage of vague contours. Conrad employs this concept to help interpret such clinical phenomena as recurring utterances.

CONCLUSION

UNANSWERED QUESTIONS

Aphasia is so broad an area and touches so many other areas and disciplines that, of necessity, some have received inordinately brief mention in this study. Such subjects as the learning of language

and the relationship between thought and speech are essential components in the consideration of aphasia.

In addition to the questions of localization and classification, there are many unanswered questions in aphasia. Critchley[13] believes that eventually involvement of the personality and/or the intellect will be shown in aphasics. A more precise analysis of the aphasias and of congenital aphasia in particular is needed. In addition, the relationship between speech dissolution and ontogeny remains to be evaluated. Of special significance is the relationship of the speech defect to "pre-morbid" habits of speech. Critchley[13] recalls pointedly Jackson's emphasis on "...the kind of brain in which the reduction occurs...."

PSYCHIATRY AND APHASIA

In furthering our knowledge of the neuronal patterns and mechanisms of aphasia, neurologists have obtained greater clarification of neurophysiologic organization. The processes of aphasia reach close to psychiatry, too. Speech and thought are intimately associated. Contrastive linguistics show an important relationship "...between the syntax of a particular language and the thought-processes of those that use the language."[13]

Freud's book, *On Aphasia,*[16] recognizes the continuum between this neurologic subject and psychiatry and psychoanalysis.[27] The close reader can see that this text foreshadows the emergence of psychoanalysis. "The idea that disturbances of function similar to those caused by brain lesions occur in the healthy person under conditions of fatigue and lack of attention...was to prove of far-reaching importance in psychopathology."[27]

Nevertheless, there is much still to be learned about aphasia, for none of the theories has had general acceptance.[17] The mechanisms of speech and aphasia still remain as challenging problems despite the century that has elapsed since Broca's enlightened studies.

Bibliography: (1) Krieg, W. J. S.: Functional Neuroanatomy, ed. 2, New York, Blakiston, 1953, pp. 388-390. (2) Goldstein, H., and Cameron, H.: A New Mental Mensuration Method for the Motor and Sensory Aphasic, Pennsylvania M. J. *62*:1513, 1959. (3) Wechsler, I. S.: A Textbook of Clinical Neurology, ed. 7, Philadelphia, Saunders, 1952, pp. 320-329. (4) Conrad, K.: New Problems of Aphasia, Brain *77*:491, 1954. (5) Brown, J. R.: Some Clinical Aspects of Aphasia, Ann. Otol. Rhin. & Laryng. *69*:1214, 1960. (6) Ruch, T. C., and Fulton, J. F.: Medical Physiology and Biophysics: Howell's Textbook of Physiology, ed. 18, Philadelphia, Saunders, 1960, pp. 479-482. (7) Riese, W.: Semantic Aphasia: II, J. Nerv. & Ment. Dis. *128*:302, 1959. (8) Hoerner, E. F., and Horowitz, B.: Diagnosis, Prognosis, and Rehabilitation in Patients with Aphasia, J.A.M.A. *166*:1573, 1958. (9) Bay, E., cited in Riese, W.: *op. cit.* (ref. 7). (10) Bucy, P. C., in Tice, F., and Sloan, L. H.: Practice of Medicine, vol. 9, Hagerstown, Md., Prior, 1959, pp. 600-605. (11) Wood, N. E.: The Child with Aphasia, Journal-Lancet *79*:315, 1959. (12) Benton, A. L., and Joynt, R. J.: Early Descriptions of Aphasia, A.M.A. Arch. Neurol. *3*:205, 1960. (13) Critchley, M.: Jacksonian Ideas and the Future, with Special Reference to Aphasia, Brit. M. J. *2*:6, 1960. (14) Schuell, H.: Clinical Findings in Aphasia, Journal-Lancet *80*:482, 1960. (15) Schuell, H., and Jenkins, J. J.: The Nature of Language Deficit in Aphasia, Psychol. Rev. *66*:45, 1959. (16) Freud, S.: On Aphasia, New York, Internat. Univ. Press, 1953. (17) Penfield, W., and Roberts, L.: Speech and Brain-Mechanisms, Princeton, N. J., Princeton Univ. Press, 1959. (18) House, E. L., and Pansky, B.: A Functional Approach to Neuroanatomy, New York, McGraw-Hill, 1960, pp. 431-433. (19) Solomon, A.: An Unusual Receptive Aphasia as a Manifesta-

tion of Temporal-Lobe Epilepsy, New England J. Med. *257*:313, 1957. (20) Landau, W. M.; Goldstein, R., and Kleffner, F. R.: Congenital Aphasia, Neurology *10*:915, 1960. (21) Weinstein, S.: Experimental Analysis of an Attempt to Improve Speech in Cases of Expressive Aphasia, Neurology *9*:632, 1959. (22) Tikofsky, R. S.; Kooi, K. A., and Thomas, M. H.: Electroencephalographic Findings and Recovery from Aphasia, Neurology *10*:154, 1960. (23) Cameron, H.: Rationalizing Aphasic Personality, Am. Assoc. Indust. Nurses J. *7*:14, 1959. (24) Moser, D.: An Understanding Approach to the Aphasic Patient, Am. J. Nursing *61*:52, 1961. (25) Strauss, A. A.: Aphasia in Children, Am. J. Phys. Med. *33*:93, 1954. (26) Levin, M.: The Levels of the Nervous System and Their Capacity to Function Independently of Each Other, J. Nerv. & Ment. Dis. *132*:75, 1961. (27) Stengel, E., in Freud, S.: *op. cit.* (ref. 16), pp. ix-xv.

sensory deprivation

SIGNIFICANCE OF INVESTIGATIONS

BACKGROUND

At birth and throughout his life an individual is the recipient of constant stimulation from the environment which structures "reality" for him. "The sense of reality and reality testing are central themes for psychiatrists, just as an understanding of the physiology of perception has been called the basis of psychology."[1] Numerous investigations have been undertaken to obtain a more adequate understanding of sensory stimulation in the development of neuronal organization, human behavior and psychic integration. In addition, as a research tool, sensory deprivation studies offer limitless opportunities for exploration.

Following the pioneer work of Hebb,[2] who ingeniously employed sensory deprivation to study perception, considerable knowledge has been acquired by investigators pursuing this exciting new research path. Anticipated space flights newly emphasize the problems of isolation stress.[3] Explorers, shipwrecked sailors and prisoners have personally described marked changes occurring under conditions of isolation.[4-6] These changes include affect disturbances, vivid imagery, sometimes in the form of delusions and bizarre hallucinations, and deterioration in ability to think and reason.[4,6]

APPLICATIONS OF EXPERIMENTAL FINDINGS

Hebb's studies in sensory deprivation were first reported by his collaborator Bexton and associates[7] in 1954. The following year, Hebb[2] reviewed basic research in the physiologic nature of learning, emotion, thinking and intelligence, which showed a clear relevance to clinical problems and has influenced psychiatric and psychologic thinking.[2] Investigation indicates that a constant sensory bombardment is essential to activation of the reticular system, which in turn generates the continuing reaction on which normal function of the brain depends.[8,9] This may account for the impairment of brain activity in a monotonous unchanging environment. It may also be relevant to the technique of indoctrinating prisoners (brainwashing), which involves deliberate impoverishment of the subject's sensory life.[10] This present review is undertaken to report the significant aspects of this rapidly expanding area of investigation.

THE EXPERIMENTAL SITUATION

DEFINITION AND CONSIDERATIONS

There is considerable disagreement among investigators on the significant features and conditions of experimentation in sensory deprivation.[11] Although "sensory deprivation" is the most popular term, "social isolation,"[12] "perceptual isolation," "reduced sensory input," "deafferentation" and "interference with reality contact" are employed, among others.[13] The diversity of terms suggests the research problem involved. "...for a conscious human, the *absolute* elimination of *any* sensory input, save for special modalities within very narrow limits *(e.g.,* visible light) is impossible...."[14]

Which senses are crucial to deprivation studies,[13] whether relative or absolute,[8,14] short-term or long-term,[15] are among the many variables underscoring the need for precise delineation of methodology in any sensory-deprivation experiment and interpretation of results. The experimental setup requires definition of the "...relevant physical, physiological, psychological and social conditions...."[16] Similarly, in reports from his laboratory, Davis[12] suggests that social isolation and concomitant reduction in kinesthetic cues must be considered in addition to the sensory deprivation *per se.*

EXPERIMENTAL TECHNIQUES

The experimental techniques adopted by investigators in studying sensory deprivation may be considered in three general categories:[5]

1. "Attempts to reduce the absolute level of intensity of all sensory stimuli...."[5] (Lilly[17] almost completely immersed nude subjects in a water tank. They breathed through a blacked-out face mask.)
2. "Attempts to reduce the patterning of stimuli...."[5] (Vernon and Hoffman[18] placed subjects in a lightproof floating room "...through which there was an 80-db sound loss.")
3. Attempts to utilize "The imposed structuring of stimuli...."[5] (Wexler used monotonous "unvarying and repetitive physical stimuli...not reduced in absolute level of intensity.")[5]

THE NATURE OF CHANGE

TYPES OF CHANGE

As already indicated, "Marked differences in experimental procedures and variables studied make it extremely difficult to compare these studies or even to be sure that all of the experimenters were concerned with the same phenomena."[19] Because of the variation in reactions of different patients

in the same experimental situations, however, the changes observed in sensory deprivation studies "...suggested a method of testing human behavior and human thought processes...."[5]

Michaels reports that "...under sensory deprivation, the individual may become apathetic, aggressive, and even confused."[20] Occasionally, anxiety or fear of panic proportions occurs, but generally the affective response is described as boredom, restlessness and irritability.[13] During experiments in "Cognitive and Physiological Effects of Perceptual Isolation," conducted at McGill University,[8] impaired performance and an inability to concentrate were observed. Many became disoriented, showing a strong susceptibility to hallucinatory phenomena and visual object distortion. In other studies examination of patients in post-isolation states disclosed a mixed state of mental acuity and physical lethargy,[14] fatigue, confusion and disorientation.[13]

CHEMICAL CHANGES

Observations on laboratory mice, in a reduced-stimulus environment, show a reduced cerebral phospholipid metabolism. However, the exact relationship of these biochemical changes to the observed aberrant behavior is not known.[3] In catecholamine studies performed in 10 male volunteers, a rise in epinephrine and norepinephrine excretion has been observed during sensory deprivation.[21] These studies of stress situations illustrate a difficult area of research—the problem of correlating behavioral changes with biochemistry.

HALLUCINATIONS—DISCUSSION AND INTERPRETATION

That the stress effect of sensory deprivation may be appreciable is illustrated by the reported development of acute psychosis in two obsessive-compulsive patients under less stringent experimental conditions.[22] Perhaps the most striking observation in the investigative reports on sensory deprivation was the emergence of visual hallucinations which Freedman and Greenblatt[19] prefer to call "imagery," as less connotative of mental illness. Shurley[14] considered the extreme range of "mental imagery" one of the most dramatic findings in his studies.

Some of the hallucinatory activity resembled the effects of mescal.[2] Geometric designs and patterns showing considerable movement were reported.[8] Content of hallucinations, however, was not confined to the visual type; auditory and kinesthetic hallucinations also were reported. One subject reported "an electric shock." Although some subjects experienced a pleasant, blissful state, Lilly and Shurley[23] report no addiction. In volunteer college men, Goldberger and Holt report dreams, depersonalization, disturbance of body image, loss of time-orientation and a "...decline in the ability to concentrate and engage in normal, directed thought...."[24]

Davis[12] and his group found that social contact lessens the effect of sensory deprivation. His study of the mental aberrations of 10 male strangers (to each other) exposed to sensory deprivation are listed in Fig. 1.

Subjects	Analogies	Daydreams	Fantasies	Pseudosomatic Delusions	Illusions	Hallucinations
A	×	×				XB. III
B	×	×	×	×		
D		×			×	
E	×					
H	×	×		×	×	
L						
M	×		×		×	
R		×				XB. III
S						
T	×	×	×			XA,B. III
	—	—	—	—	—	
	6	6	3	2	3	3

Fig. 1 "Mental Aberrations in Male Strangers" Experiment*

Type III hallucination classified, according to Vernon:[25] " 'structured integrated scenes which sometimes are even animated.' In addition, 'A' denotes that the subject had insight that his 'hallucination' was not real, 'B' denotes the absence of such insight."[12]

*From Davis, J. M., et al.: Arch. Gen. Psychiat. 5:84, 1961.

In order to study the basic factors involved in hallucinations and other mental phenomena occurring in sensory deprivation, Davis[26] and his co-workers employed concomitant random visual stimulation. Although mental aberrations were not prevented in this experiment, the results suggest consideration of meaningfulness of input.

"A theoretical formulation is proposed which would attribute the perceptual distortions [in sensory deprivation] to the organism's continuous automatic search for order in a non-ordered perceptual environment."[19] The same investigators state: "In the absence or ambiguity of external cues, regression and fantasy are encouraged; the subject must look within himself to define the situation."[19] Rosenzweig[27] considers that under normal conditions, "...conscious perception of the activities originating in the affect system" are inhibited. Under conditions of severe regression or sensory curtailment as in overwhelming anxiety, sleep or sensory isolation, hallucinations could develop.

THE CLINICAL SITUATION

GENERAL

Results from sensory-deprivation experiments suggest that certain isolated and immobilized medical and surgical patients develop psychotic manifestations from "...silence, darkness, and loneliness rather than solely from organic or toxic causes."[4] Heron[8] calls attention to the reported changes in perceptual function where the afferent input has been reduced, as in amputees.[28,29] Leiderman[30] has tabulated a summary of mental abnormalities observed in medical-surgical patients as shown in Fig. 2.

Case	Age, Yr.	Manifest Anxiety	Disorientation			Delusions	Hallucinations		
			Person	Place	Time		Visual	Auditory	Somesthetic
Poliomyelitis, composite of 9 cases†	11–13	×	×	×	×	×	×	×	×
Other neurological diseases									
1. Polyneuropathy	60	×		×		×	×		
2. Polyneuropathy	29	×		×		×	×	×	
Orthopedic disorders									
3. Fractured hip	85	×		×	×	×			
4. Arthritis	75	×			×	×			
Surgery									
5. Cholecystectomy	76	×		×	×	×			
Cardiac disorders									
6. Congestive failure	62	×		×	×				
Blindness									
7. Acute glaucoma	71	×		×	×	×	×		
Deafness, composite of 17 cases‡	19–23	×			?				
Public health									
8. Car driving fatigue	18						×		

†Mendelson, J. H., and Foley, J. M.[31]
‡Mendelson, J. H., et al.[32]

Fig. 2 Mental Abnormalities as Complications of Medical or Surgical Conditions.*

*Leiderman, H., et al.: A.M.A. Arch. Int. Med. 101:389, 1958.

VISUAL AND HEARING DISTURBANCES

Linn[33] and associates have reported delirium in 20 of 21 consecutive ophthalmologic patients following bilateral senile cataract extraction and a severe disturbance in 13 cases. According to Weisman and Hackett,[34] although the clinical picture of "black-patch delirium" resembles other forms of postoperative delirium, the precipitating factor is total deprivation of vision. A doctor-patient relationship which serves to further the patient's reality-orientation may prevent or relieve the delirium.

The spatial, vivid, highly colored dreams of the congenitally deaf[32] suggest a certain relevance to the imagery, fantasies and hallucinatory experiences observed in sensory deprivation. Characteristic differences in dreams of the deaf were less pronounced in those subjects whose deafness developed after age 5.[32]

THE EFFECT OF MONOTONY

Autobiographical reports of explorers suggest that sometimes it was the lack of change in quantitation of sensory input that "...seemed like a force which would destroy them."[6] The stress of prolonged exposure to monotonous environment produces deleterious effects, notably impaired thinking, visual perceptive disturbances and visual and auditory hallucinations. The need of human beings for a changing sensory environment may have a practical application in safety programs for industry and regulations for long-distance drivers.

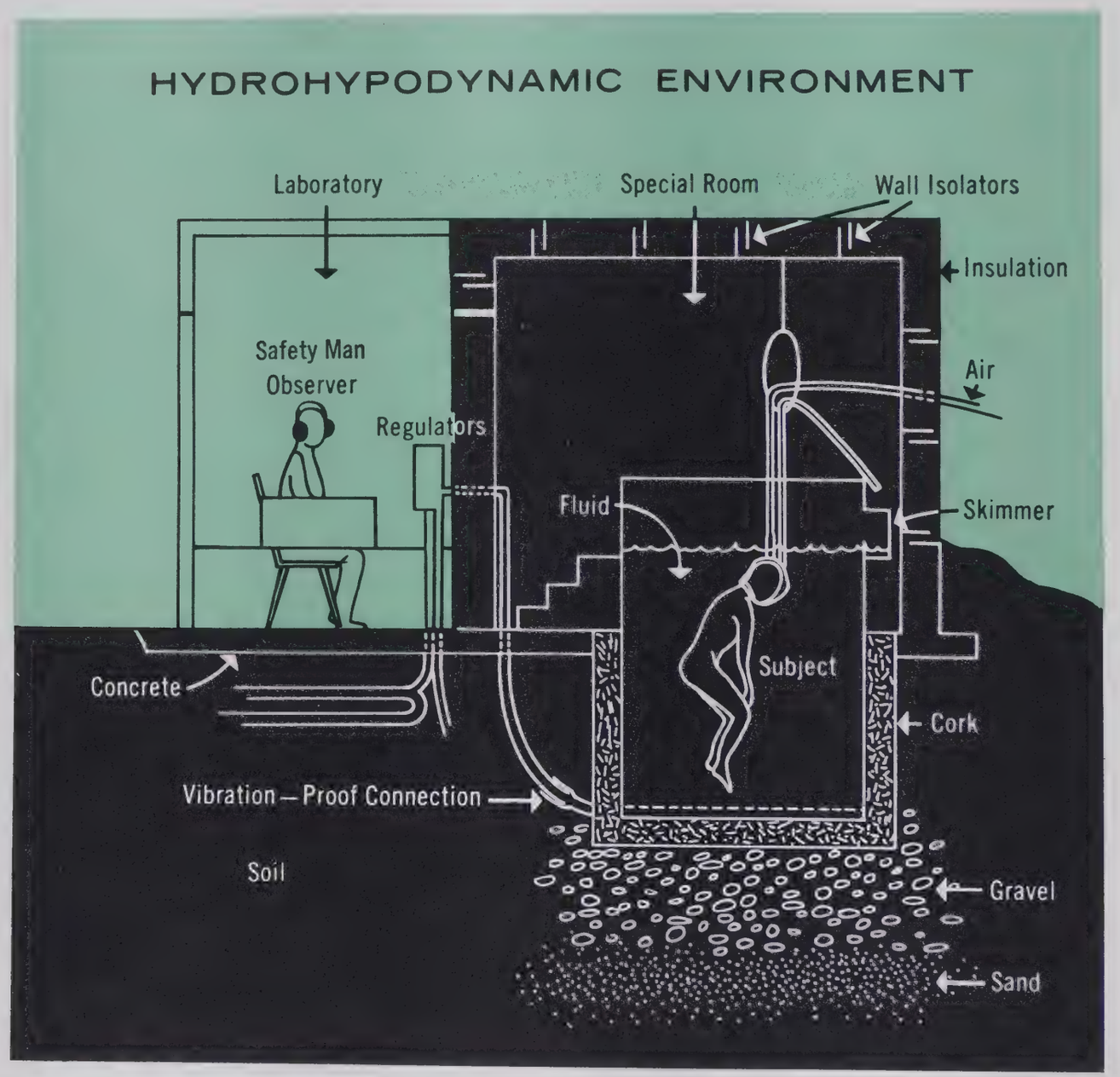


Fig. 3 Laboratory for Study of Profound Sensory Isolation*

*From Shurley, J. T.: Am. J. Psychiat. 117:539, 1960.

SIGNIFICANCE OF FINDINGS AND OBSERVATIONS IN SENSORY DEPRIVATION

The significance of sensory deprivation studies has reached and touched upon many disciplines. Within the physical limitations of this review, the bearing on physiology, psychology, psychiatry and some of the social implications of these findings are discussed.

NEUROPHYSIOLOGY

The results of sensory deprivation (intellectual blocking, emotional disturbances, hallucinations) have supplied additional evidence to support the changing physiologic concept of the central nervous system. That it could no longer be viewed as a switchboard mechanism has been shown particularly by studies emphasizing the significance of afferent stimulation in the sleep and arousal mechanism.[35,36]

In order to study the importance of sensory information on nonsensory functions, Sprague, Chambers and Stellar[37] severed the sensory projections to the forebrain in cats by electrolytic currents which produced lesions in the lateral midbrain. Symptoms obtained from such *anatomic* and *physiologic* sensory deprivation were marked generalized sensory deficit, lack of affect, stereotyped hyperexploratory and exaggerated oral activities. From their observations, these investigators concluded that a "rich and varied" afferent input is essential to adequate adaptive behavior.

Reasoning from data obtained from animal and human studies, Lindsley[38] has suggested that some of the behavioral findings in (a) sensory deprivation (b) sensory overload, and (c) sensory distortion, result from a change in balance between cortical activity and the reticular activating system function. In explaining the emotional changes in sensory deprivation, another view[39] implicates hypothalamic mechanisms, suggesting that "...the sensory, parasympathetic and sympathetic branches of the nervous system are related."

MAN AND HIS ENVIRONMENT

A major implication of sensory deprivation research pertains to the role of stimuli in growth and development of individual personality. As Hebb[2] has stated, "...psychological development is fully dependent on stimulation from the environment. Without it, intelligence does not develop normally, and the personality is grossly atypical." In the young especially, deprivation is a major factor, causing later permanent adaptational hardship in the adult organism. Bruner[40] proposes that rich perceptual environment in early experience stimulates the development of "...learning—that deprivation prevents it." Apparently, psychological integrity of the individual continues to depend on normal sensory environment.[13] Hebb's studies and those of others suggest that sensory deprivation leaves the subject less able to meet adaptational demands.[41]

PSYCHIATRY

The influence of psychology on psychiatry may be considerable as a result of sensory deprivation studies. It has been shown "...fairly conclusively that living organisms, the human organism in particular, not only are unable to tolerate extended periods of inactivity but, under such conditions, experience hunger for stimulation and change."[42] Monotony may therefore be "...as damaging as trauma."[43] Fenichel,[44] in discussing the psychology of boredom, has emphasized the stimulus-hunger and the dissatisfaction with available stimuli. It would thus appear that "...a concept of 'heterostasis'—the tendency of organisms to depart from balance and seek new stimuli which, in turn, lead to new levels of adaptation"[43]—might well be supplementary to Cannon's theory of homeostasis.[45]

The different individual responses to interference with reality contact[24] and to the effects of such activities as high-altitude flying[46] suggest sensory deprivation as an experimental method for studying inner resources and developmental patterns.[46] This of course has more direct application to the analytic situation.

THERAPY

In a study of the effects of partial perceptual isolation, Azima and Cramer reported "A beneficial therapeutic effect...in the five depressed cases, in two this effect was permanent."[22] In another clinical report[47] of a pilot study on 30 psychiatric patients exposed to partial sensory deprivation, the "greater than chance" favorable results suggest psychotherapeutic possibilities of sensory deprivation. Investigators have frequently commented on the similarity between sensory deprivation and the psychoanalytic situation.[15,19] Freud[48] had remarked on the significance of sensory reception and its importance in awareness of reality in the outside world. Stimulus-deprivation furthers "regression,"[49] apparently facilitating access to unconscious material.[13] According to Rapaport,[15] "Psychoanalytic technique explicitly recognizes that a reduction of contact with reality is necessary to permit id derivatives to rise to consciousness." He cites as a clinically significant illustration the treatment of a patient in the changed environment of a psychiatric hospital.[15] Sensory deprivation studies point not only to the usefulness of this technique in the psychoanalytic situation, but also to the need for adequate social and sensory contact, in the care of both the mentally and the physically ill patient. Thus it has been observed that family contacts with children in respirators have decreased "...the cognitively debilitating effects of reduced stimulation...."[40]

SPECIAL SITUATIONS

The so-called brainwashing techniques, or solitary confinement as in concentration camps, utilize sensory deprivation as part of their technique,[15] the former removing the stimulus-nutriment of allegiances and beliefs,[50] the latter the nutriment of the structures underlying self-respect, dignity and identity.[51] Other than sensory deprivation, another aspect in brainwashing is the imposed control of external stimuli. Davis[12] calls attention to the fact that since "...the patient or prisoner is cut off from his normal *supportive* environment and is in a fear-provoking situation," he may develop hallucinations or delirium in spite of stimulation.

CONCLUSION – FUTURE DIRECTIONS

The vistas of experimental study in sensory deprivation are ever-broadening. This is a new field and there are many essential studies still to be done and questions to be resolved in respect to the experimental approach. Kubie[52] emphasizes the fallacy of identifying "afferent 'inflow' with 'awareness of sensations.'" In sensory-deprivation experiments, he feels there must be "...full awareness that we do not yet know the exact extent to which the afferent impulses in the different modalities are actually interfered with or cut off."[52] In his opinion, the delineation of the experimentally isolated portions of the *total* afferent inflow—unconscious as well as conscious—will provide sounder conclusions.

In spite of present limitations, experiments in sensory deprivation are giving new insights into the individual and the broad range of his psychophysiologic phenomena. These investigations are providing the means of studying "...discrete elements in the complicated, interconnected patterns and sequences underlying even the simplest human act or experience."[14] As such, they contribute to a better understanding of human behavior.

Perhaps what presently emerges from sensory deprivation studies as especially significant to the practice of medicine has been most succinctly stated by Davis: "It appears that what the brain needs for normal functioning is not quantity or change in sensation *per se,* but a continuous meaningful contact with the outside world."[26]

Bibliography: (1) Cobb, S., in Solomon, P., *et al.*: Sensory Deprivation, Cambridge, Mass., Harvard Univ. Press, 1961, p. xviii. (2) Hebb, D. O.: The Mammal and His Environment, Am. J. Psychiat. *111*:826, 1955. (3) Wase, A. W., and Christensen, J.: Stimulus Deprivation and Phospholipid Metabolism in Cerebral Tissue, Arch. Gen. Psychiat. *2*:171, 1960. (4) Solomon, P., *et al.*: *op. cit.* (ref. 1), pp. 1, 4, 5. (5) Wexler, D.; Mendelson, J.; Leiderman, P. H., and Solomon, P.: Sensory Deprivation, A.M.A. Arch. Neurol. & Psychiat. *79*:225, 1958. (6) Solomon, P.; Leiderman, P. H.; Mendelson, J., and Wexler, D.: Sensory Deprivation, Am. J. Psychiat. *114*:357, 1957. (7) Bexton, W. H.; Heron, W., and Scott, T. H.: Effects of Decreased Variation in the Sensory Environment, Canad. J. Psychol. *8*:70, 1954. (8) Heron, W., in Solomon, P., *et al.*: *op. cit.* (ref. 1), pp. 6-33. (9) Claes, E., cited by Heron, W.: *ibid.* (10) Hinkle, L. E., Jr., and Wolff, H. G.: Communist Interrogation and Indoctrination of "Enemies of the States," A.M.A. Arch. Neurol. & Psychiat. *76*:115, 1956. (11) Vernon, J., and Hoffman, J., cited in Wexler, D.; Mendelson, J.; Leiderman, P. H., and Solomon, P.: *op. cit.* (ref. 5). (12) Davis, J. M.; McCourt, W. F.; Courtney, J., and Solomon, P.: Sensory Deprivation, Arch. Gen. Psychiat. *5*:84, 1961. (13) Kubzansky, P. E., and Leiderman, P. H., in Solomon, P., *et al.*: *op. cit.* (ref. 1), pp. 221-238. (14) Shurley, J. T.: Profound Experimental Sensory Isolation, Am. J. Psychiat. *117*:539, 1960. (15) Rapaport, D.: The Theory of Ego Autonomy: A Generalization, Bull. Menninger Clin. *22*:13, 1958. (16) Lilly, J. C., and Shurley, J. T., cited in Shurley, J. T.: *op. cit.* (ref. 14). (17) Lilly, J. C.: Mental Effects of Reduction of Ordinary Levels of Physical Stimuli on Intact, Healthy Persons, Psychiat. Res. Rep. *5*:1, 1956. (18) Vernon, J., and Hoffman, J.: Effect of Sensory Deprivation on Learning Rate in Human Beings, Science *123*:1074, 1956. (19) Freedman, S. J., and Greenblatt, M.: Studies in Human Isolation, WADC Tech. Rep. *59*:266 (Sept.) 1959. (20) Michaels, J. J., in Arieti, S.: American Handbook of Psychiatry, New York, Basic Books, Inc., vol. 1, 1959, pp. 353-377. (21) Mendelson, J., *et al.*: Catechol Amine Excretion and Behavior During Sensory Deprivation, Arch. Gen. Psychiat., *2*:147, 1960. (22) Azima, H., and Cramer, F. J.: Effects of Partial Perceptual Isolation in Mentally Disturbed Individuals, Dis. Nerv. System *17*:117, 1956. (23) Lilly, J. C., and Shurley, J. T., in Flaherty, B. E.: Psychophysiological Aspects of Space Flight, New York, Columbia Univ. Press, 1961, pp. 238-247. (24) Goldberger, L., and Holt, R. R.: Experimental Interference with Reality Contact (Perceptual Isolation): Method and Group Results, J. Nerv. & Ment. Dis. *127*:99, 1958. (25) Vernon, J. A.; McGill, T. E., and Schiffman, H., cited by Davis, J. M., *et al.*: *op. cit.* (ref. 12). (26) Davis, J. M.; McCourt, W. F., and Solomon, P.: The Effect of Visual Stimulation on Hallucinations and Other Mental Experiences During Sensory Deprivation, Am. J. Psychiat. *116*:889, 1960. (27) Rosenzweig, N.: The Affect System: Foresight and Fantasy, J. Nerv. & Ment. Dis. *127*:113, 1958. (28) Teuber, H. L.; Krieger, H. P., and Bender, M. B.,

cited by Heron, W.: *op. cit.* (ref. 8). (29) Haber, W. B., cited by Heron, W.: *op. cit.* (ref. 8). (30) Leiderman, H.; Mendelson, J. H.; Wexler, D., and Solomon, P.: Sensory Deprivation: Clinical Aspects, A.M.A. Arch. Int. Med. *101*:389, 1958. (31) Mendelson, J. H., and Foley, J. M.: An Abnormality of Mental Function Affecting Patients with Poliomyelitis in a Tank-Type Respirator, Tr. Am. Neurol. A. *81*:134, 1956. (32) Mendelson, J. H.; Siger, L., and Solomon, P.: Psychiatric Observations on Congenital and Acquired Deafness: Symbolic and Perceptual Processes in Dreams, Am. J. Psychiat. *116*:883, 1960. (33) Linn, L., *et al.*: Patterns of Behavior Disturbance Following Cataract Extraction, Am. J. Psychiat. *110*:281, 1953. (34) Weisman, A. D., and Hackett, T. P.: Psychosis After Eye Surgery, New England J. Med. *258*:1284, 1958. (35) Magoun, H. W., cited in Kubzansky, P. E., and Leiderman, P. H.: *op. cit.* (ref. 13), p. 235. (36) Granit, R.; Galambos, R.; Pribram, K.; Magoun, H. W., *et al.*, cited by Bruner, J. S., in Solomon, P., *et al.*: *op. cit.* (ref. 1), p. 196. (37) Sprague, J. M.; Chambers, W. W., and Stellar, E.: Attentive, Affective, and Adaptive Behavior in the Cat, Science *133*:165, 1961. (38) Lindsley, D. B., in Solomon, P., *et al.*: *op. cit.* (ref. 1), pp. 174-194. (39) Gellhorn, E., cited in Kubzansky, P. E., and Leiderman, P. H., *op. cit.* (ref. 13), pp. 234, 235. (40) Bruner, J. S., in Solomon, P., *et al.*: *op. cit.* (ref. 1), pp. 195-207. (41) Hebb, D. O., and White, R. W., cited in Kubzansky, P. E., and Leiderman, P. H., *op. cit.* (ref. 13), pp. 236, 237. (42) Hebb, D. O.; Lilly, J. C.; Heron, W., *et al.*, cited by Sargent, H. D., and Mayman, M., in Arieti, S.: American Handbook of Psychiatry, New York, Basic Books, Inc., vol. 2, 1959, p. 1717. (43) Sargent, H. D., and Mayman, M.: *ibid.*, pp. 1711-1732. (44) Fenichel, O., in Rapaport, D.: Organization and Pathology of Thought, New York, Columbia Univ. Press, 1951, pp. 349-361. (45) Cannon, W. B., cited by Sargent, H. D., and Mayman, M.: *op. cit.*, p. 1717. (46) Bennett, A. M. H., in Solomon, P., *et al.*: *op. cit.* (ref. 1), pp. 161-173. (47) Gibby, R. G.; Adams, H. B., and Carrera, R. N.: Therapeutic Changes in Psychiatric Patients Following Partial Sensory Deprivation: A Pilot Study, Arch. Gen. Psychiat. *3*:33, 1960. (48) Freud, S., in Rapaport, D.: *op. cit.* (ref. 44), pp. 315-328. (49) Fisher, C., cited in Kubzansky, P. E., and Leiderman, P. H., *op. cit.* (ref. 13), p. 231. (50) Lifton, R. J., cited in Rapaport, D.: *op. cit.* (ref. 15), p. 26. (51) Bettelheim, B.: Individual and Mass Behavior in Extreme Situations, J. Abnorm. & Social Psychol. *38*:417, 1943. (52) Kubie, L. S., in Solomon, P., *et al.*: *op. cit.* (ref. 1), pp. 208-220.

Prepared by Schering
as a service to the medical profession

TR-422

PRINTED IN U.S.A.